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NATIONAL HEART, BLOOD VESSEL, LUNG, AND BLOOD PROGRAM

FIRST ANNUAL REPORT OF THE DIRECTOR OF THE NATIONAL HEART AND LUNG INSTITUTE

FEBRUARY 13, 1974

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
National Institutes of Health
National Heart and Lung Institute

FIRST ANNUAL REPORT OF THE DIRECTOR OF THE NATIONAL HEART AND LUNG INSTITUTE

SUBMITTED TO
THE PRESIDENT OF THE UNITED STATES
FOR TRANSMITTAL TO
THE CONGRESS OF THE UNITED STATES
IN ACCORDANCE WITH PUBLIC LAW 92-423

FEBRUARY 13, 1974

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
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DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
BETHESDA, MARYLAND 20014

NATIONAL HEART AND LUNG INSTITUTE

February 13, 1974

The President
The White House
Washington, D. C.

Dear Mr. President:

I am pleased to submit to you for transmittal to Congress the first annual report on the National Heart, Blood Vessel, Lung, and Blood Program. It highlights the activities, progress, and accomplishments of the Program during the past calendar year and updates the Program Plan completed in May 1973. This report is prepared in response to Section 413(b) of the National Heart, Blood Vessel, Lung, and Blood Act of 1972 (Public Law 92-423, 86 STAT 679).

The National Heart, Blood Vessel, Lung, and Blood Program is gaining momentum and interest. Contributing to its implementation, planning, and evaluation are thousands of scientists, physicians, and other health professionals across the United States; the National Heart and Lung Institute and its Advisory Council; other bureaus, institutes, and divisions of the National Institutes of Health; Federal agencies and departments both within and without the Department of Health, Education, and Welfare; and voluntary organizations and interested and committed citizens.

The Program gives special emphasis to prevention of heart attacks, the greatest killer in our nation; high blood pressure education, since millions of our citizens do not know that they have it and that it can be treated; expansion of the attack on lung diseases, a heretofore neglected area; and the development of a national blood policy, a critical national need. Also, the previous emphasis on the control of sickle cell disease will be continued.

We strongly agree with you that "Keeping People Healthy" is one of our nation's most important goals for the 1970's, and appreciate your pledge to give "increased attention to the fight against diseases of the heart, blood vessels, and lung which account for more than half of the deaths in this country."

Respectfully,

Theodore Cooper

Theodore Cooper, M. D.
Director

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I. INTRODUCTION

I. INTRODUCTION

The United States, despite its high state of technology, lags behind many other Western nations in the health of its citizens. In fact, it ranks 24th in the world with respect to life expectancy for men. The high mortality from heart and blood vessel diseases is the major contributing factor to this shortened life expectancy.

The quality and composition of our environment are important to the maintenance of health--the air we breathe, the water we drink, the food we eat. We can live only a few minutes without oxygen, a few days without water, and a few weeks without food. Many of the diseases addressed by the National Program on Heart, Blood Vessel, Lung, and Blood Diseases are known to be related to the quality of our environment. The impact of these diseases, as compared to that of other diseases, is summarized in Table 1.

Table 1. Ranking of Diseases According to Health Impact, United States, 1971

DISEASE	DAYS OF BED DISABILITY		HOSPITAL DISCHARGES		HOSPITAL DAYS	
	RANK	DAYS*	RANK	NUMBER*	RANK	DAYS*
Influenza & pneumonia	1	206,241	–	–	–	–
Upper respiratory	2	164,840*	2	1,311	11	3,444
**Heart disease	3	93,137	1	1,390	1	17,921
Arthritis	4	57,539	12	217	9	3,837
Mental disorders	5	41,965	5	695	3	15,273
Fractures & dislocations	6	35,625	3	1,249	2	17,097
Malignant neoplasms (Cancer)	7	32,374	6	646	4	7,786
Impairments of back & spine	8	31,895	–	–	–	–
**Hypertensive without heart involvement	9	27,476	9	314	12	2,780
**Bronchitis	10	27,388	–	–	–	–
**Asthma	11	25,997	–	–	–	–
**Cerebrovascular disease	12	24,762	11	264	7	5,128
Paralysis	13	24,052	–	–	–	–
Diabetes	14	23,739	10	280	10	3,498
Impairments of lower extremities	15	20,986	–	–	–	–
Ulcer	16	17,569	8	492	8	5,245
**Emphysema	17	13,124	–	–	–	–
Hernia	18	11,948	4	726	8	4,835
Gall bladder	19	11,892	7	530	5	6,922
Absence of extremities	20	7,347	–	–	–	–
Impairments of upper extremities	21	5,491	–	–	–	–

– Data not available
* In thousands
** Addressed by National Program

SOURCE: Unpublished Data from the National Center for Health Statistics

Through the mandate provided by the National Heart, Blood Vessel, Lung, and Blood Act of 1972, the nation's scientific and medical resources are beginning to be mobilized in a national collaboration of Federal, non-Federal, and private organizations, as well as citizens at large.

The initial Program Plan,* dated May 1, 1973, which was forwarded to the President and Congress, presented a broad program strategy for achieving improved health. This strategy is:

> ". . . to marshall national resources for promoting and restoring health, and for preventing and treating disease more effectively by:
>
> - Initiating an ordered sequence of coordinated program activities ranging from the acquisition of new knowledge to demonstration and control programs in the health care setting of the community
>
> - Providing adequate program evaluation before the application of existing knowledge to health care delivery systems
>
> - Evaluating the impact of implemented programs on the health of the American people."

Within the broad strategy outlined above and in compliance with the National Heart, Blood Vessel, Lung, and Blood Act of 1972, a multifaceted National Program has taken shape. The scope of the evolving program ranges from fundamental studies of molecules inside single cells within the human system to studies of effects of pharmacological agents, to development and evaluation of new types of therapy involving advanced bioengineering concepts. It also includes studies of patient attitudes, behavioral studies, and investigations dealing with man's ability to cope with underwater and space environments, reaching into future vistas of mankind.

In implementing this broad strategy, a number of basic factors having impact on all program components for the future, as well as the present were considered

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*The National Heart, Blood Vessel, Lung, and Blood Program was presented in five volumes; DHEW Publication Numbers are shown below:

Volume I.	National Heart and Lung Institute Summary (NIH 73-515)
Volume II.	Report of the National Heart and Lung Advisory Council (NIH 73-516)
Volume III.	Report of the Panel Chairmen (NIH 73-517)
Volume IV.	Panel Reports (NIH 73-518 - 73-521)
Volume V.	Program Analysis (NIH 73-522 - 73-524)

and dealt with initially. During the past eight months since the Plan was initiated, six major strategic actions have been taken by the National Heart and Lung Institute:

1. Reorganization of the Institute's programs.
2. Promotion of collaborative efforts.
3. Creation of an Office of Prevention, Control, and Education.
4. Development of guidelines for national centers.
5. Analysis and evaluation of actions in the initial Plan.
6. Review and assessment of goals, progress, and future challenges.

These actions are outlined briefly below:

REORGANIZATION NHLI activities have broadened considerably under the National Program. To meet these new responsibilities, the Institute has reorganized its entire program into divisions corresponding to the major heart, lung, and blood disease areas. This development is discussed in greater detail in Chapter VI.

COLLABORATION To most effectively utilize all of our national resources to combat heart, blood vessel, lung, and blood diseases, the NHLI has initiated and fostered collaborative programs involving many sectors of society. This activity has been promoted through the Interagency Technical Committee as well as other mechanisms, as elaborated in Chapter IV.

PREVENTION, CONTROL, AND EDUCATION To implement a special provision of the National Heart, Blood Vessel, Lung, and Blood Act, the NHLI has created an Office of Prevention, Control, and Education. This office is responsible for disseminating health information and for public education activities. It is also responsible for the prevention and control programs as outlined in Chapter III.

NATIONAL CENTERS To expedite the further development of the National Program throughout the country, explicit criteria and guidelines for the establishment of national research and demonstration centers have been developed and released for use by potential applicants. This action is described further in Chapter VI.

ANALYSIS OF ACTIONS IN INITIAL PLAN

During the past year, the NHLI has made a careful study of the material upon which the Actions in the initial Plan were based. As a result, a revised program structure of 22 elements (10 for heart and blood vessel diseases, 8 for lung diseases, and 4 for blood diseases and blood resources) was developed as illustrated in Table 2. This revised program structure is used in this report, in lieu of the 17-element structure of the initial Plan, to describe progress, update the Plan, and allocate proposed fiscal resources. Also, as a part of this study, each Action of the initial Plan has been examined for its relative importance to the total program. This report reflects several minor shifts in emphasis resulting from this analysis.

REVIEW AND ASSESSMENT OF GOALS, PROGRESS, CHALLENGES

Finally, with respect to the item above, a thorough review and assessment of Program Goals, Recent Progress, and Future Challenges have been carried out in each program area. The results of this assessment are reflected mainly in Chapter III. Actions of the initial Plan have been updated and some additional items have been included in the updated Plan.

Table 2. National Heart, Blood Vessel, Lung, and Blood Program Structure

HEART AND BLOOD VESSEL DISEASES

1. Arteriosclerosis
2. Hypertension
3. Cerebrovascular Disease
4. Coronary Heart Disease
5. Peripheral Vascular Diseases
6. Arrhythmias
7. Heart Failure and Shock
8. Congenital and Rheumatic Heart Diseases
9. Cardiomyopathy and Infections of the Heart
10. Circulatory Assistance

LUNG DISEASES

1. Structure and Function of the Lung
2. Pediatric Pulmonary Diseases
3. Emphysema and Chronic Bronchitis
4. Fibrotic and Immunologic Lung Diseases
5. Respiratory Failure
6. Pulmonary Vascular Diseases
7. Inhalation Diseases
8. Respiratory Assistance

BLOOD DISEASES AND BLOOD RESOURCES

1. Bleeding and Clotting Disorders
2. Sickle Cell Disease and Related Disorders of the Red Blood Cell
3. Biomaterials
4. Blood Resources

This report on the National Program is the first annual report on the activities, progress, and accomplishments in the Program and is the first update of the 5-Year National Plan. It supersedes Volume I of the original Plan. In addition to shedding more light on the six strategic actions described above, the report covers the following topics:

Chapter II.	Highlights of the National Program
Chapter III.	Status of Program and Updated Five-Year Plan
Chapter IV.	Program Coordination
Chapter V.	Manpower Development
Chapter VI.	Implementation of Other Provisions of the Act
Chapter VII.	Resource Allocation Plan.

The National Heart, Blood Vessel, Lung, and Blood Act of 1972 is reproduced in Appendix A. Definitions, full descriptions, and the mortality and morbidity impact of major problem areas have been reprinted from the National Heart and Lung Institute Summary (May 1, 1973) of the National Program and are presented in Appendix B with definitions of new problem areas added at the end.

Insofar as possible, the report is presented in nontechnical language in order to communicate with interested laymen who may be unfamiliar with medical terminology. Where such terminology is unavoidable, effort has been made to provide clarification in the text of the report. Reference to the definitions and discussions of major heart, blood vessel, lung, and blood problem areas contained in Appendix B will also be helpful to the lay reader in understanding the concepts discussed in this report.

II. HIGHLIGHTS OF THE NATIONAL PROGRAM

II. HIGHLIGHTS OF THE NATIONAL PROGRAM

Collectively, heart, blood vessel, lung, and blood diseases cause more deaths than all other diseases in the United States combined. They have a devastating effect on the health of our citizens as well as on the nation's economy. More than 30 million Americans suffer from these diseases. Their impact in terms of national economic loss has been estimated at more than $40 billion a year. These figures, while impressive in terms of identifying the problem, fail to convey the seriousness of the social impact of these diseases--the dimensions of suffering, grief, disability, stress and hardship, and the effects these diseases have on the patient and the patient's family.

Why do these diseases overwhelm our current health care system, and is there hope for a solution to the problem? The principal reason why they overwhelm our health care system is that we lack the necessary understanding to deal with them effectively. This understanding can be obtained through research. A second reason is that the results of medical research are sometimes not applied to the health care system as expeditiously as they might be. Thus, further medical research and the application of the knowledge gained through research offer substantial hope of reducing the devastating effects of heart, blood vessel, lung, and blood diseases in the future. Accordingly, the National Heart, Blood Vessel, Lung, and Blood Program focuses primarily on two types of efforts: (1) Research Programs, and (2) Prevention, Control, and Education Programs to bridge the gap between research findings and clinical application. Currently, the expenditures for research on these problems represent less than one percent of the total costs for these diseases. For instance, in the case of heart and blood vessel diseases, the estimated annual cost to the economy is more than $30 billion, while the total Federal expenditure for research in this area in FY 72 was about $200 million.* Yet, medical research is the wisest investment that the nation can make to insure further progress in the attack against heart, blood vessel, lung, and blood diseases. Thus, the common interest of everyone in our society dictates a high priority for the further development of the comprehensive National Heart, Blood Vessel, Lung, and Blood Program.

*Volume I, National Heart and Lung Institute Summary, May 1973, p. 17.

A conceptual strategy for the National Program Plan was presented nearly one year ago in the National Heart and Lung Institute Summary, referred to earlier. This initial strategy provided the first approximation of the direction the program would take, its underlying principles, and its method of implementation. The strategy was not complete in concept or in operational detail--nor was it intended to be at this early stage. Each year as we gain more experience and knowledge in the planning, implementation, and evaluation of a major national program for biomedical research, the conceptual and operational aspects of the program will become clearer and more precise. In the initial program strategy, three underlying principles were outlined as summarized below:

- The long-range goal must be to improve the health of the American people.
- Programs for achieving this goal must be based on an orderly progression of sequenced activities from acquisition of fundamental knowledge to the application of existing knowledge.
- Evaluation of the use of knowledge--both before its application in health care delivery and after to determine its impact on the health of the American people--will be the key to meeting national health goals.

The major planning problem addressed during this past year has been how to translate abstract goals and principles, conceived at a policy-making level, into meaningful program activities involving thousands of individuals. In formulating an attack on this problem, we have reexamined the above principles and found them still viable. We have extended these principles conceptually into a more complete strategy. And we have begun to implement this strategy operationally. The updated program strategy, outlined below, gives increased attention to the importance of the social and physical aspects of our human environment and their relationship to health and disease. The operational steps taken to implement this strategy are described in Chapters III, IV, V, and VI of this report, and the estimated resources to put the plan into effect are presented in Chapter VII.

In seeking solutions to the pressing health problems of heart, blood vessel, lung, and blood diseases, we are giving special recognition to the social and physical aspects of the human environment and their role in the development of these diseases. Also, the importance of the context of the total human environment to the success of the National Program is being considered in the planning, implementation, evaluation, and coordination of the Program.

Our modern technological society offers many choices of life style both for everyday working life and for the increasingly available leisure time. We live in an age characterized by specialization of labor, sophisticated machinery, complex systems of organization, and mass production. In communicating with the public and the health professions, the Program emphasizes how the choice of life style and physical environment, by individuals as well as communities, in fact may imply a choice of future health or disease of the heart and the lungs. Current and future program plans stress how disease might be prevented before the onset of

catastrophic illness which may be beyond the reach even of modern medical technology. Currently, the National Program gives special emphasis to five program areas described in detail in Chapter III and highlighted below:

- Prevention of heart attacks--the greatest killer in our nation
- High blood pressure education--millions of our citizens do not know that they have high blood pressure, that it may lead to serious complications such as stroke and death, and that treatment is available
- Expansion of the attack on lung diseases--a heretofore neglected area
- Development of a national blood policy--a critical national need
- Methods of controlling sickle cell disease.

Social change, brought about by the increasing use of rapid communication and transportation systems, has radically altered leisure and work activities, resulting in new health problems which fall within the scope of the National Heart, Blood Vessel, Lung, and Blood Program.

Changing attitudes are directing our attention to long-neglected disease problems particularly prevalent in certain population groups. Sickle cell disease, one of these problems, is receiving special emphasis in the National Program. Such programs, in addition to the need for medical expertise, require a high degree of knowledge about the special needs and desires of these patients. The great expense of providing available medical treatment, such as Factor VIII for patients with hemophilia, creates drastic social changes for the family of the victim. It may, in fact, condemn the family to life-long poverty. Social change is causing increasing numbers of elderly citizens, many of whom have cardiovascular or respiratory problems, to be without the aid of or proximity to their families in times of need.

Socioeconomic factors play a role in the development of many diseases. While poverty is associated with increased infant, maternal, and overall mortality, the general affluence in the United States is thought to be associated with the high mortality rate from coronary heart disease and heart attacks.

Social isolation is a problem in many parts of the United States, both in urban and rural areas. This often prevents the National Program from reaching those people who need it most. The Institute is paying particular attention to developing lines of communication with community health resources and developing education and demonstration programs to alert the medical profession and the public to new methods of disease control and treatment in the local community. Specifically, the Institute is developing cooperative programs with Federal and non-Federal health agencies for the purpose of controlling, and in the long-term preventing, heart, blood vessel, lung, and blood diseases. One example is the National High Blood Pressure Education Program, discussed in Chapter III under Prevention, Control, and Education.

Social mobility, particularly geographic mobility, creates problems which limit the timing of National Program efforts. An average of 18 percent of the total U. S. population moves annually. This places restrictions on the length of time available for follow-up of patients participating in clinical studies to determine the benefits of new treatments, such as the modification of diet in the therapy of heart disease. It further poses managerial problems in carrying out well-controlled studies in large free-living populations. The Institute is careful to take these factors into consideration in its planning of long-range clinical trials, such as the Multiple Risk Factor Intervention Trial discussed in the section on Arteriosclerosis in Chapter III.

Our American culture and the quality of life in the United States appear important in increasing a person's susceptibility to heart and lung disease. For instance, in Denmark, Norway, and Sweden, the death rate from coronary heart disease for men under the age of 55 is less than half that for the same age group in the United States. In Japan it is one-sixth that in our country. These international statistics indicate that the high death rates from coronary heart disease in the United States are neither necessary nor inevitable. Research has identified a number of factors which appear important in increasing a person's susceptibility to heart and lung disease. Programs are being developed to modify these factors without disrupting our way of life. Specifically, the National Program emphasizes research, control, and education efforts on how heart and vascular disease might be prevented through changes in life style, and how such changes can be most effectively implemented. Good health is everyone's major source of wealth and happiness. The American public is generally not aware of the extent to which the individual can contribute to maintenance of good health and prevention of disease. Programs are underway to explore, develop, and evaluate the most effective means of motivating the public as a whole to take voluntary action which may be helpful in promoting personal health, preventing disease, and assuring prompt treatment of disease before a crisis situation develops.

Urbanization and life stresses in general are being studied to determine how these factors affect the development of disease. Behavioral studies have indicated that certain types of individuals are more prone than others to develop heart and lung disease under conditions of similar stress. Periods of mental and environmental stress may thus be associated with an increased incidence of disease. However, the exact nature of these associations remains to be defined.

In the case of lung diseases, the social habit of cigarette smoking is believed to be a prime factor in the etiology or exacerbation of both chronic bronchitis and emphysema--two chronic obstructive lung diseases which are on the increase in the United States. Smoking also contributes to environmental lung diseases and hypersensitivity lung diseases. Up to 20 percent of smokers have chronic obstructive lung disease, and almost all afflicted patients are smokers. Thus, one of the major goals of the National Program in the field of lung diseases is to modify the smoking habits of persons at risk of developing lung diseases and to extend successful anti-smoking programs to the general population. The Program also addresses the problem of pollution brought on by the technological revolution in the United States. This is a well-recognized problem in lung disease, and one which may be regulated by society. The choice is ours.

In developing and evaluating highly sophisticated therapeutic modalities such as artificial circulatory assistance, the National Program has given a prominent place to nonmedical aspects of the human environment. Examples are public attitudes and social, ethical, legal, and other factors important in assessing the public impact and in ensuring the acceptance of the new treatment when it is introduced in practice. Behavioral scientists, ethicists, lawyers, economists, educational experts, and interested laymen are cooperating in the Program to identify nonmedical issues that may help or hinder this and other research, prevention, and treatment programs.

The human environment also plays an important role in the National Program efforts to deal with the difficult problem of national blood resources. This entire program depends upon the willingness of human beings to donate blood for use by other human beings. High quality blood and blood products are essential to effectively treat many diseases as well as to save the lives of injured individuals. To be able to supply sufficient quantities of any given blood product on a moment's notice requires many steps, from recruiting the donor to collecting the blood, separating it into its components, detecting and eliminating disease-causing agents, matching the components for compatibility with the recipient's blood, and administering the blood or blood component to the patient in a safe manner. In the United States, many different organizations are responsible for these operations. A major problem with the present system is the lack of uniform quality control of blood donations. The NHLI, in cooperation with a number of Federal and non-Federal agencies, is striving for an all-volunteer blood system.

A comprehensive account of recent progress and future challenges for all program areas addressed by the National Program is presented in Chapter III of this report. Since Chapter III is rather technical in content, the use of medical terminology is unavoidable. To provide the lay reader with an overview of prominent program developments, highlights of recent progress and future challenges are presented below in lay language for each of heart and blood vessel diseases, lung diseases, and blood diseases and blood resources.

HIGHLIGHTS: HEART AND BLOOD VESSEL DISEASES

Highlights of recent progress and future challenges in research, prevention, control, and education programs include:

Prevention of Heart Attacks -Identification of Risk Factors

There are approximately 1,250,000 heart attacks in America each year. The five major and well-established risk factors for coronary artery disease and heart attacks are: age, male sex, high levels of blood lipids, high blood pressure, and cigarette smoking. The latter three can be modified, and for two of these we know that a decrease in the factor results in reduced risk. Cessation of cigarette smoking will decrease the enhanced risk of heart

attacks among smokers. Reduction of moderate or severe hypertension reduces devastating complications such as stroke, heart failure, and kidney failure.

Prevention of Heart Attacks -Modification of Risk Factors

The Institute has implemented three large-scale clinical trials to evaluate the cardiovascular effects of risk factor modification. Within this decade, we should know the impact of lowering the levels of blood lipids on heart attacks and the impact of controlling high blood pressure on heart attacks, as well as the impact of controlling simultaneously the three major risk factors: high levels of blood lipids, high blood pressure, and cigarette smoking.

Prevention of Heart Attacks -Determination of Blood Lipids

Accurate and precise determination of blood lipids is essential for effective and efficient risk factor detection and management. Review of operating conditions in United States laboratories reveals a wide and unacceptable variation in the accuracy and precision of blood lipid (cholesterol and triglyceride) measurements. Quick-kit methods are totally unacceptable. Many of the large automated laboratories are employing techniques that yield values 10 to 40 percent too high. Over the last two years the NHLI has evaluated available technology and developed with industry a rapid, inexpensive, accurate, and precise method for determining cholesterol and triglyceride levels.

Prevention of Heart Attacks -Behavioral Studies

Current studies demonstrate that chronic and asymptomatic disorders such as arteriosclerosis (hardening of the arteries) and high blood pressure are not easily brought and held under control. Health attitudes and lack of motivation often lead to failures in compliance with changes in life style or with diets and drugs in attempting to change risk factors. Evidence from smoking clinics and from diabetics or hypertensives under treatment indicates that these behavioral elements rather than our understanding of risk factors may prove to be the limiting factors in our ability to prevent coronary heart disease.

Prevention of Heart Attacks -Role of Public Education

Public education is of primary importance in the prevention of coronary heart disease. Major steps have been taken to educate the general public regarding the causes and prevention of coronary heart disease. An example is the Seattle Heart Watch which includes a series of television programs produced with the University of Washington. Among topics covered in the series are dietary alteration, exercise programs, signs of impending heart attack, and whom to contact concerning an attack.

Heart Attacks -The Role of Blood Lipids

Epidemiological studies have established strong positive associations with high levels of blood lipids (cholesterol) and with age relative to the incidence of heart attacks. A recent study with a special X-ray technique has emphasized these associations in terms of the pathological changes in the coronary arteries.

Heart Attacks -A New Sudden Cardiac Death Syndrome

A previously undefined syndrome of potentially major clinical importance has been described. This new syndrome has been called the Primary Ventricular Fibrillation Syndrome or Instantaneous Death Syndrome. Clinically, those patients fortunate enough to be resuscitated following sudden collapse exhibit disturbance of heart rhythm, absence of recent or evolving myocardial infarction (death of heart muscle), presence of chronic coronary heart disease, and a very high incidence of sudden death (30 percent per year) subsequent to resuscitation. The recognition of this sudden death syndrome presents an opportunity to prevent premature deaths from coronary artery disease by preventing or controlling the disturbance in heart rhythm.

Heart Attacks -Therapy to Reduce Heart Muscle Damage

Recent investigations have shown that the patient's prognosis is directly related to the amount of dead heart muscle resulting from a heart attack. Pharmaceutical agents, oxygen therapy, and mechanical circulatory assistance are promising new therapies for limiting the amount of heart muscle damage from heart attacks.

High Blood Pressure -National Education Program

Drug therapy to control high blood pressure reduces the incidence of strokes and heart failure among persons with moderate or severe hypertension. However, only about 12 percent of hypertensives in the United States are currently receiving adequate treatment. The National High Blood Pressure Education Program, initiated in 1972, is an interagency Federal/non-Federal cooperative effort designed to bring individuals with moderate and severe hypertension under effective treatment. Sustained effective blood pressure management in such persons is expected to result in a reduction of disability and death by as much as 40 percent when compared with expected rates for untreated hypertensives.

Prevention of Heart and Blood Vessel Disease -The Framingham Heart Study

A 22-year follow-up has been completed on 5,209 participants in the Framingham study. Analysis of the data reveals that: (1) High blood pressure is the major cause of congestive heart failure, with elevations of systolic pressure ("upper" blood pressure reading) playing as great a role as diastolic pressure ("lower" blood pressure reading); (2) Cigarette smoking is a major contributor to intermittent claudication (severe cramps and pain in the muscles of the legs on walking due to insufficient blood supply) and acts independently of high blood pressure, high levels of blood lipids, or diabetic status; (3) Obesity is a risk factor in coronary heart disease, stroke, and congestive heart failure, independent of other risk factors; and (4) The quantitative influence of several risk factors acting simultaneously has been analyzed and the results published for use by clinicians in the prevention of heart disease.

Understanding Arteriosclerosis

Arteriosclerosis is responsible for about 85 percent of the deaths from heart and blood vessel diseases. Recent progress has been made in the understanding of arteriosclerosis. Certain preliminary studies of smooth muscle cells that make up the bulk of atherosclerotic plaques suggest the possibility that each plaque consists mainly of one colony of cells that have all arisen from a single cell of the artery wall that is ancestral for the particular plaque. While this work remains to be confirmed, it raises fundamental issues in the pathogenesis of atherosclerosis.

Studies of the Blood Vessel Wall

While elaborating and extending methods of culturing cells derived from human blood vessels, investigators are studying their properties to develop ways to use these cells in artificial blood vessels. The method has now been carried beyond seven generations of cells in culture as pure colonies that maintain all the basic morphological and metabolic properties of the lining of the vessels. These methods offer hope for enhancing our ability to construct artificial blood vessels compatible with the blood.

Using Computers to Detect Irregularities in the Blood Vessel Wall

Utilizing contrast angiograms (a special X-ray technique) together with computerized analysis of the images produced, it has been possible to obtain sensitive and highly reproducible diagnosis of changes in the blood vessel wall resulting from disease. This technique can facilitate early detection of cardiovascular disease.

Noninvasive Instrumentation

Instrumentation is probably the most important single constraint to the effective prevention of clinical complications of arteriosclerosis. Convenient, preferably noninvasive, specific, and sensitive instrumentation for the diagnosis and monitoring of atherosclerotic plaques is needed. This would allow studies of the relationship of risk factor levels to actual development of arteriosclerosis in the individual patient and provide a precise statement of what the total identified risk factors mean for that individual. Of most importance, such instrumentation could monitor the development of arteriosclerosis and measure the therapeutic effect of changing one or more of the risk factors. The ability to safely determine the results of a therapy or life style change on the development of arteriosclerosis, without having to wait for a crisis event such as heart attack or death, would also enormously decrease the rigorous demands and costs of clinical trials.

Mechanical Circulatory Assistance

Mechanical circulatory assistance with intra-aortic balloon counterpulsation was introduced into clinical studies about a decade ago. Its exact role and effect in patients with acute heart attack had to be determined. Studies showed that this form of mechanical left heart assist could temporarily reverse shock even when refractory to all forms of medical therapy. This assistance permits further diagnostic studies and possible surgical therapy in patients who would otherwise be unable to withstand these procedures.

However, the overall impact of this form of therapy remained to be determined, especially in relation to the morbidity and mortality in those patients less critically ill. Recent studies in patients have now shown a definite reduction of infarct size associated with the use of mechanical left heart assist.

Implantable Heart Assist Device

A totally implantable left heart assist device may have a significant future in terms of acute and chronic cardiac insufficiency. In recent experiments, a device has performed successfully in calves. In several acute implantations, excellent results were obtained in terms of the amount of blood put out by the heart, heart rates, and blood pressure. These implantations have demonstrated functionally the potential of these devices for individuals requiring left ventricular assist.

HIGHLIGHTS: LUNG DISEASES

Highlights of recent progress and future challenges in research, prevention, control, and education programs include:

Pediatric Lung Disease -Detection Before Birth

Hyaline membrane disease (HMD) is a disorder of newborn babies characterized by the immaturity of the lung. It usually occurs in premature infants, starts within hours of birth, and frequently leads to death within a few days. Without special treatment, over 50 percent of babies with this disease will die. If death from this disease could be eliminated, the infant mortality rate in this country might be reduced to a level comparable to the best in the world. Current therapy is available for treatment of hyaline membrane disease. However, delay in diagnosis contributes greatly to its high morbidity and mortality. A major diagnostic breakthrough has occurred which allows detection of hyaline membrane disease before birth. This technique, which involves sampling amniotic fluid, promises to result in exciting new therapeutic and preventive measures.

Pediatric Lung Disease -New Therapy

Hyaline membrane disease is characterized by collapse of the oxygen-exchanging portions of the lung resulting in extreme difficulty in breathing and in death, as noted above. The course of HMD is relatively rapid, and survival is usually determined within a matter of days to 1 to 2 weeks. Therapeutic efforts have focused on methods of maintaining the airways open and allowing adequate oxygenation of the blood. Until recently, the usual therapy for HMD consisted of artificial ventilation and other intensive care usually available in large hospital centers. Unfortunately, this was not sufficient. Many infants still died

from this disease. The therapeutic breakthrough that long has eluded investigators may now have been achieved. A provocatively simple technique, albeit one that requires scrupulously attentive patient care, has resulted in a survival rate of up to 90 percent in some studies. This therapy is continuous positive airway pressure (CPAP) and is used in conjunction with artificial ventilation.

Asthma -Diagnosis in the Asymptomatic Child

Asthma, which affects more than 8 million Americans, could be prevented or treated while still reversible if it were diagnosed sufficiently early. A diagnostic test has been developed recently and is currently undergoing evaluation. This test involves exposing patients to a substance called methacholine. It may allow physicians to predict, perhaps years before symptoms develop, whether an individual is a potential victim of asthma. This potentially important diagnostic tool should permit already available therapeutic and preventive measures to be initiated early.

Chronic Obstructive Lung Disease -Early Detection

Chronic bronchitis and emphysema are the major chronic obstructive pulmonary diseases (COPD). A new, and potentially more sensitive, method has been developed for early detection of changes in lung function and structure which appear to be the first sign of chronic obstructive pulmonary disease. This method (measurement of closing volume) is now being used on selected populations to determine its usefulness as a mass screening test.

Chronic Obstructive Lung Disease -Risk Factors

Emphysema is the fastest growing cause of death in the United States. There are many different kinds of emphysema, none of which is well understood. Cigarette smoking has long been recognized as a major risk factor for emphysema, but attempts to identify other causes and risk factors have frequently ended in failure. New lines of research have been opened up by the recent discovery of a genetic basis for one type of emphysema. Other risk factors may soon be found as well.

Understanding Lung Disease

It has been recognized that the lung is an organ with several functions which may be as complex as the liver. The structure of the lung is also very complex as it is made up of as many as 40 different cell types. Technology is now at hand to relate structure and function at the cellular level by using cell culture techniques. As this information develops, it should be possible to begin investigations into the molecular basis of lung disease--an essential step toward effective prevention and treatment.

Artificial Lung To Treat Respiratory Failure

It has been estimated that at least 150,000 adult patients a year suffer from respiratory failure. Despite the availability of intensive care units, the lung function of these patients on occasion continues to deteriorate. Approximately 40 percent of these patients die. Therefore, patients with potentially reversible lung disorders still die because of a need for short-term respiratory augmentation. An artificial lung has been developed and tested that oxygenates the blood external to the body. This device can provide long-term (days) support without serious blood damage. In recent years, clinical studies have shown that these membrane oxygenators can be used successfully to provide partial respiratory support for patients with acute respiratory failure.

HIGHLIGHTS: BLOOD DISEASES AND BLOOD RESOURCES

Highlights of recent progress and future challenges in research, prevention, control, and education programs include:

Dissolving Blood Clots in the Lung

A clinical trial has been completed of an enzyme capable of dissolving blood clots in the lung. Results indicate that the enzyme streptokinase (a relatively inexpensive and available preparation) dissolves blood clots in the lung just as effectively as the more widely publicized urokinase (another enzyme preparation), which is quite difficult to obtain. These results are important to the development of more readily available treatment of thromboembolic diseases.

A New Technique to Measure Abnormal Tendency of Blood to Clot

A hypercoagulable state in which the blood is more likely to clot than normally contributes to a variety of diseases including development of arteriosclerosis and heart attacks. Methods to adequately measure or characterize this state have been lacking. A method of sufficient sensitivity and specificity has now been developed which will make possible earlier initiation of appropriate therapy.

Sickle Cell Disease -Prevention of Sickle Cell Crisis

While clinical trials to evaluate urea as an anti-sickling agent have shown that it is not effective in the treatment of the sickle crisis, evaluation of other anti-sickling agents continues. Preliminary studies with sodium cyanate are quite promising.

A Cooperative Study Group composed of researchers and clinicians has been formed to collaborate and work together to answer research and clinical questions in sickle cell disease. This group will form the nidus for a larger group which will address itself to hemolytic diseases in general.

Five sickle cell disease centers and eleven screening and education clinics have been added to continue research and demonstration efforts (bringing the total to 15 centers and 26 clinics).

Hemophilia -Improved Treatment

A procedure has been developed which will improve production of Factor VIII, which is used to stop bleeding in hemophiliac patients. This procedure will enable blood banks and laboratories throughout the country to obtain more potent and more uniform Factor VIII from donor blood. Use of this procedure will improve hemophilia therapy and also permit more efficient use of donated blood and plasma.

Hepatitis -Transmission through Blood Transfusion

Two large studies on the epidemiology of hepatitis B infection are nearing completion, including one in New York City of blood donors found to be carriers of hepatitis antigen. Newer, more sensitive detection systems for hepatitis B are being developed and compared. A study of the efficacy of hepatitis B immune globulin in the treatment or prevention of hepatitis B infection has shown that this agent is not effective in the treatment of acute fulminant type B viral hepatitis.

Preventing the Rejection of Transplanted Organs

Investigators are pursuing means of preventing the sensitization of the transplant patient by lowering or attempting to eliminate histocompatibility-antigens (HL-A) in transfused blood. Platelet (one of the formed elements in blood) studies are in progress to determine the indications for HL-A typing in platelet transfusions. Studies of in vitro methods for removing HL-A from blood will be completed this year to be followed by clinical trials on renal dialysis patients.

Development of Artificial Materials Which Will Not Harm Blood

Important progress has been made in developing techniques to impart blood compatibility to materials for artificial organs in contact with blood. As one example, a class of "springy" polypropylene has been synthesized with unique tissue-like physical properties for potential prosthetic applications. The technology now exists to graft blood compatible materials, such as hydrogels, to the polypropylene surface and thus greatly increase its potential for biologic use.

Safe Materials for Blood Bags

A method has been developed and evaluated which accurately detects the amount of plasticizer DEHP (di-2-ethylhexylphthalate), a substance leached out of blood bags during blood storage. It should now be possible to assess more readily the clinical significance of the presence of DEHP in tissues and body fluids of transfused patients.

III. STATUS OF PROGRAM AND UPDATED FIVE-YEAR PLAN

III. STATUS OF PROGRAM AND UPDATED FIVE-YEAR PLAN

The current status of the National Heart and Lung Institute Program and the Program Plan over the next five years are presented together in this chapter. The overall goals of the National Program are to: promote health, prevent disease, treat disease, and restore health. To advance toward these goals the Institute, through the National Heart, Blood Vessel, Lung, and Blood Program, is focusing primarily on two types of program efforts:

- Research, and
- Prevention, Control, and Education.

The Research programs deal largely with the development of new knowledge and the testing and evaluation of existing knowledge. The Prevention, Control, and Education programs deal with the application and dissemination of knowledge already developed and evaluated through research, but not yet effectively applied toward the prevention, control, and treatment of disease. These Prevention, Control, and Education programs are an essential link between biomedical research and health care. Their purpose is not to deliver health services but rather to improve and expedite the transmission of fundamental research advances to the public and to medical practitioners and thereby help to promote the health of our citizens.

For clarity and emphasis, Research programs and Prevention, Control, and Education programs are discussed separately in this chapter. The Institute gives special emphasis to the need for ensuring that the results of research are utilized for the prevention and control of disease; hence, where appropriate in this chapter, Research programs are cross-referenced with Prevention, Control, and Education programs.

In 1972, the Institute initiated an intensive planning effort in response to the National Heart, Blood Vessel, Lung, and Blood Act. This planning effort involved the participation of four advisory Panels and their Task Groups drawn from universities, medical schools, hospitals, and other institutions throughout the United States. Advice and recommendations were also sought from the National Heart and

Lung Advisory Council, the Interagency Technical Committee on Heart, Blood Vessel, Lung, and Blood Diseases and Blood Resources, and representatives of non-Federal and voluntary organizations with related programs. Ongoing program efforts as well as means for expanding successful past research efforts were also considered.

The purpose of this planning effort was to formulate a National Program for heart, blood vessel, lung, and blood diseases and blood resource problems. The initial Program Plan developed during this planning effort was published in May 1973. Since that time, the Institute has carefully reviewed and assessed the projects and activities of the National Program. The program structure developed initially has been revised (see Table 2, Chapter I). This revised structure includes 10 program areas for Heart and Blood Vessel Diseases, 8 for Lung Diseases, and 4 for Blood Diseases and Blood Resources. The current status and updated 5-year Plan for all of these program areas are presented in this chapter in the Research section and the Prevention, Control, and Education section.

For each program area, the goals, actions, and schedules for implementation, as set forth initially, have been reviewed and updated. Recent progress and future challenges for each program area have been identified. The results of this review are presented here in detail for each program area. Program Goals are correlated with Recent Progress and Future Challenges, and specific Actions and Schedules for implementation of these Actions are set forth. This comprehensive discussion of the National Program should provide the basis for continued monitoring, annual review, and updating of the 5-year Program Plan.

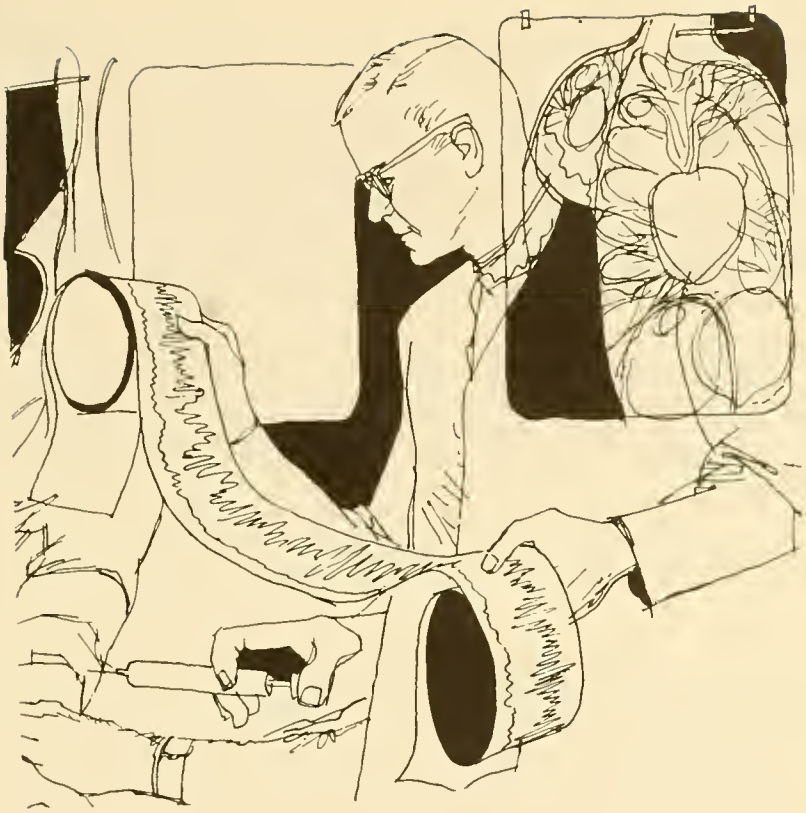
RESEARCH

Programs of research are fundamental to the National Heart, Blood Vessel, Lung, and Blood Program. Future developments in the prevention, treatment, and control of disease are dependent upon basic knowledge of the life processes, how and why these change with disease, and how such changes might be controlled or reversed. For instance, we cannot prevent heart attacks until we know more about the mechanisms of arteriosclerosis, how those mechanisms may be accelerated by risk factors, and how the process of arteriosclerosis might be arrested or reversed. Also through research, the knowledge necessary for promoting and restoring health will be developed. Only when we fully understand, for instance, the normal and abnormal functioning of the lung will we be able to promote conditions conducive to good health.

The Institute supports a broad range of fundamental and clinical research in order to develop this essential information base for achieving the overall goals of the National Program. By strongly supporting research, the first and basic step in the sequence from acquisition of fundamental knowledge through testing and evaluation to application of that knowledge, the Institute can provide for the orderly progression of activities as conceived in the program strategy cited earlier.

In this section, research programs are discussed separately for Heart and Blood Vessel Diseases, Lung Diseases, and Blood Diseases and Blood Resources. Although discussed separately, these diseases are linked one to the other. As stated by the Panel Chairmen during the planning effort, "Disordered biological functions seldom involve a single area. As examples, pulmonary embolism begins with thrombosis and involves the lung and its circulation as well as the heart. Effective delivery of oxygen to the tissue depends on the lung, the heart, the amount, type, and functional states of the hemoglobin, and the peripheral circulation." Research efforts in one program area will impact on research efforts in other program areas. The activities in Coronary Heart Disease will have an impact on the program areas of Arrhythmias and Heart Failure and Shock. The recent progress and future challenges in research and the scheduled Actions in Cerebrovascular Disease are closely related to those for Arteriosclerosis and Hypertension. Research advances in understanding Thromboembolic Disorders will be important in clarifying the role of these disorders in precipitating heart attacks and their relationship to the development of Arteriosclerosis. Developments through research on blood compatible prostheses will have an impact on many techniques and devices developed for heart, blood vessel, and lung diseases. Research on the Structure and Function of the Lung will be important in decreasing the mortality and morbidity resulting from Emphysema and Chronic Bronchitis. Thus, the research programs in all areas are closely related. Appropriately, cross-references among the program areas are provided in this Research section to elucidate some of the complexities of research.

In FY 75, the highest priority program areas in research are: Arteriosclerosis, Hypertension, Coronary Heart Disease, Structure and Function of the Lung, Emphysema and Chronic Bronchitis, Bleeding and Clotting Disorders, Sickle Cell Disease, and Blood Resources. These programs are selected as high priority because research advances in these areas are expected to have the greatest impact on developing our information base on heart, blood vessel, lung, and blood diseases; on preventing and controlling these diseases; and on promoting and restoring the health of our citizens.



HEART AND BLOOD VESSEL DISEASES

The Legislative Act charges the Institute to conduct research programs to investigate the epidemiology and etiology of heart and blood vessel diseases, and to study the basic biological mechanisms and processes involved in normal and abnormal phenomena. An impressive array of opportunities and needs can be pursued in the heart and blood vessel (cardiovascular) disease area at this time. The approaches that appear most promising, most efficient, and are most needed to develop new knowledge about heart and blood vessel diseases are summarized here.

Cardiovascular disease is by far our number one health problem in the United States. In 1971, an estimated 1,022,000 Americans died from heart and blood vessel diseases, i.e., more than 53 percent of deaths from all causes. Of these deaths, heart attack was responsible for 676,000, and stroke for 208,000. Currently, an estimated 27,710,000 Americans have some major form of heart and blood vessel disease; 22,340,000 have hypertension; 3,870,000, coronary heart disease; 1,700,000, rheumatic heart disease; and 1,650,000, stroke.

The Institute planning effort relied heavily on the Heart and Blood Vessel Diseases Panel and Task group participants, representing many universities, medical schools, hospitals, and other institutions throughout the United States. Advice and recommendations were also sought from the National Heart and Lung Advisory Council, the Interagency Technical Committee on Heart, Blood Vessel, Lung, and Blood Diseases and Blood Resources, and representatives of non-Federal and voluntary organizations with related programs. The National Program in Heart and Blood Vessel Diseases, developed with participation from the above groups, was outlined in the National Heart and Lung Institute Summary (Volume I) of the National Heart, Blood Vessel, Lung, and Blood Program which was published on May 1, 1973.

The updated National Program, presented here, represents an assessment and orderly expansion of NHLI activities in the cardiovascular area in response to the mandate of the National Heart, Blood Vessel, Lung, and Blood Act. The updated heart and blood vessel research programs of the National Heart and Lung Institute deal with ten program areas:

1. Arteriosclerosis
2. Hypertension
3. Cerebrovascular Disease
4. Coronary Heart Disease
5. Peripheral Vascular Diseases
6. Arrhythmias
7. Heart Failure and Shock
8. Congenital and Rheumatic Heart Diseases
9. Cardiomyopathy and Infections of the Heart
10. Circulatory Assistance.

The first nine program areas were identified separately in 1973. The tenth program area, Circulatory Assistance, was included initially under the section on Heart Failure and Shock, and is presented separately for emphasis in this updated Plan.

Following its review and evaluation of program activities, the Institute has modified some Actions and has increased the total number of research Actions in heart and blood vessel diseases from 28 in the initial Plan to 45 in the updated Plan. Most of this increase occurs in the program areas of Arteriosclerosis and Coronary Heart Disease. These additional Actions will be important in expanding the Institute's efforts to prevent heart attacks, the greatest single cause of death in the United States.

1. ARTERIOSCLEROSIS

PROGRAM GOALS

Arteriosclerosis is by far the most common serious disease affecting man in Western society. It is responsible for about 85 percent of the deaths from heart and blood vessel diseases in the United States. It is a slow, progressive disease that sets the stage for heart attacks, heart failure, and strokes. To understand the origins and control of arteriosclerosis is the primary objective of the National Program in heart and blood vessel diseases.

Recent research has developed a significant amount of new knowledge about the causes and development of arteriosclerosis. Significant positive statistical associations have been demonstrated between arteriosclerotic disease and high blood lipids, high blood pressure, heavy consumption of cigarettes, physical inactivity, personality type, and other factors. However, we do not yet completely understand the causal relationship of these variables to arteriosclerosis. Current studies on molecular and tissue interactions promise to help explain the development of arteriosclerosis and offer opportunities for its prevention.

Obviously, preventing the events leading to atherosclerotic plaque formation in the arteries would be better and far less costly than attempting to treat the resultant vascular disease and its sequelae. The Institute has many leads to prevention and better understanding of arteriosclerosis, some of which come from research on metabolism, normal and abnormal structure and function of the arteries, and genetic and environmental factors which influence atherogenesis. The NHLI concurs with the priority recommendations of the Heart and Blood Vessel Diseases Panel, which was convened for developing the initial plan, to "define more completely the pathogenesis of atherosclerosis" and "to conduct controlled clinical trials." Accordingly, the National Program gives high priority to continued emphasis on these activities.

- Our overall goal in arteriosclerosis is to obtain a better understanding of its basic process and to improve the prevention, diagnosis, and treatment of the process and its sequelae.

RECENT PROGRESS

Strong efforts to find solutions to the problem of arteriosclerosis are being made in fundamental research, nutritional studies, and clinical investigations. As a result of these efforts, the Institute can report significant progress in adding new knowledge and techniques to help in our attack against arteriosclerosis. Examples of these many detailed advances are given below.

Fundamental Research. The processes leading to the development of atherosclerosis are closely related to altered permeability of the walls of the arteries. Lipids are deposited in the wall more rapidly than they are removed. Experiments in living animals and isolated human blood vessels indicate that patterns of increased permeability which permit greater fat deposition are virtually identical to patterns of early atherosclerosis. The arterial wall is made more permeable by various hemodynamic factors such as constrictions, increased blood flow, and increased blood pressure, as well as by endothelial injury.

Studies on the transport of lipids to and from the arterial wall have been extended by the development of better techniques of isotopically tagging lipid and protein components of plasma lipoproteins to permit analyses of the mechanism of transport of these molecules into the arterial wall, either as units or in parts. Methods of determining alterations in "chemical barrier" and wall ultrastructure have been developed. Examination of the transport of lipid molecules away from the arterial wall once they have been deposited indicates this to be a complex and slow process.

The process of lipolysis (decomposition of lipids) is central to the utilization of fats by the body, whether ingested in the diet or made in the tissues, and is a major determinant of blood lipid concentrations. The part played by various enzymes in the arterial wall during this process is being explored. The arterial wall contains enzymes such as alkaline lipase (lipoprotein lipase) and acid hydrolases capable of breaking down the lipids entering the wall from the blood. Lipoprotein lipase has been the subject of intensive study almost continuously since its discovery at the NHLI 20 years ago. Scientists have now shown that there are at least two different lipases that can be liberated into blood to hasten lipid removal. One enzyme, coming from the liver, is believed to play a role in degrading lipid remnants, possibly for entry into the liver. The other acts primarily to degrade larger lipid particles, chylomicrons and very low density lipoproteins. Lipoprotein lipase is selectively absent in one human mutation (familial Type I hyperlipoproteinemia) leading to abnormal levels of lipid in the blood of these individuals. Other tissue enzymes capable of decomposing lipids have also been intensively studied this past year. New compounds have been found which may be involved in arteriosclerotic plaque formation. The previous observations on the rapid and reversible effect of insulin on lipids have been further advanced and it is now possible to study more directly the nature of the effects of insulin and adrenal hormones in the handling of fats by the body.

Hyperlipidemia (high blood lipids) is one of the major conditions associated with premature atherosclerosis, particularly coronary artery disease, and is one of the first rank problems facing American physicians, especially those engaged in preventive medicine. The NHLI has been a leader in promulgating new systems of classification and identification of causes and treatment of hyperlipidemia.

The Institute's extramural Lipid Research Clinic Program had its birthplace within the NHLI Intramural Research Division. The prevalence of and mechanisms behind the human forms of hyperlipidemia are now being studied at the 12 extramural Lipid Research Clinics (LRC's). The 12 clinics are collaborating on a protocol for central processing and evaluation of the heart, coronary, and major vessels in post-mortem examinations on LRC patients. The central pooling and processing of all pathologic material in the LRC Central Pathology Laboratory at the NHLI will allow us to gather useful clinical pathologic correlations regarding human hyperlipidemias.

In several of the Institute's Specialized Centers of Research in Arteriosclerosis, improvements are now being made in invasive and noninvasive diagnostic methods for the recognition of atherosclerotic plaques in the blood vessels. Other fundamental studies involve the development and use of nonhuman primate models for studies on the development, progression, and regression of the atherosclerotic process.

Nutrition. Nutritional factors are believed to play an important role in the development of arteriosclerosis, and studies are in progress to clarify the role of these factors. The Multiple Risk Factor Intervention Trial, currently being implemented, has a strong nutritional component with the objective of reducing elevated serum cholesterol by adherence to a lipid-lowering diet, and in certain cases, weight control and correction of obesity. In addition, reduced intake of total carbohydrate and alcohol will be advised for men with elevated triglycerides who fail to respond to the basic diet.

A detailed nutritional questionnaire and 1-day diet recall are included in the Lipid Research Clinics' prevalence studies, and a central computerized data system has been created to evaluate the role of diet in hyperlipidemia and the association of diet with the incidence of vascular disease. The relationship of nutritional factors to lipid metabolism and development of atherosclerosis is being studied by many scientists, primarily in the Institute's Specialized Centers of Research in Arteriosclerosis.

Clinical Investigations. The clinical investigations within the program on arteriosclerosis are varied, complex, and broad in scope. The recent progress highlighted here only refers to some of the major efforts underway and does not, by far, reflect the total Institute effort. The Lipid Research Clinics are initiating an in-depth study of the relatives of patients found to have primary hyperlipoproteinemia during the prevalence studies. The clinics are also finalizing a protocol to evaluate the feasibility of using placental cord blood for the early diagnosis of hyperlipidemia. A central clinical chemistry laboratory has been selected for the network of clinics collaborating in the Lipid Research Clinics Primary Prevention Trial, designed to test whether or not lipid lowering can prevent or delay the onset of manifest vascular disease. Recruitment of patients for this important clinical trial has begun.

The planning and organizational phases for another primary prevention trial, the Multiple Risk Factor Intervention Trial, have just been completed. Twenty clinics, a coordinating center, and a central EKG and chemistry laboratory for the trial have been selected.

Two extensive studies of patients with the most common form of hypercholesterolemia (hyperbetalipoproteinemia, Type II hyperlipoproteinemia) were completed in 1973 by the NHLI's Intramural Research laboratories. One study involved analysis of over 200 children born of parents with a form of familial hypercholesterolemia, which probably affects about 1 in 200 Americans. The genetic data indicated a clear-cut mode of inheritance determined by a single gene and manifested early in childhood; information about the clinical manifestations and potential for diagnosis at birth was also developed. In a companion analysis, the cardiovascular risks of this hypercholesterolemia in over 1,000 relatives of affected patients were examined. This was the most extensive such analysis ever undertaken of this genetic defect. This study provides striking evidence of the premature atherosclerotic risk of patients affected with this disorder.

In-depth genetic investigation of risk factors is being encouraged in the Specialized Centers of Research in Arteriosclerosis. A study is in progress to characterize with regard to cardiovascular risk factors the familial and genetic associations of offspring of 1,644 spouse sets who were part of the original Framingham cohort. More than 2,200 offspring have undergone evaluation to date in this study. The NHLI Twin Study has now collected data on more than 600 sets of identical twins aged 25 to 55, and preliminary results indicate major genetic determinants of the observed variability in height, weight, blood pressure, and serum cholesterol. Offspring study of the propositi of the Honolulu cohort of the Honolulu-Hiroshima-San Francisco Heart Disease Study has also begun.

The Coronary Drug Project, a secondary prevention clinical trial of lipid-altering drugs has reached an average follow-up of 58 months in a population of 8,400 men aged 30 to 64 who have had one or more myocardial infarctions prior to entry into the study. This trial has already uncovered unfavorable features of two drugs, i.e., estrogen and dextrothyroxine, and is scheduled to terminate in 18 months.

FUTURE CHALLENGES

All aspects of the study and treatment of arteriosclerosis would be greatly advanced if we had diagnostic instruments for detecting small changes in atherosclerotic plaques. The present state of technological development suggests that this is possible. Current approaches include highly sophisticated techniques such as ultrasonic methods, X-ray densitometry, and computer-assisted enhancement of complex image signals. These techniques are not yet adequate but indicate a feasible and promising technical area where rapid and successful progress can be expected.

Many needed studies of chronic arterial disease cannot be conducted in man and require the development of suitable animal models of human disease, particularly nonhuman primate models with chronic experimental arteriosclerosis and chronic experimental hypertension. These models would allow us to study the development and regression of atherosclerotic plaques, local biochemical and cellular changes in advanced plaques, and treatment of advanced plaques. Animals with spontaneous metabolic disease such as hyperbetalipoproteinemia (elevated blood lipids) or diabetes need to be bred to create resource colonies for studies of the relationship of these disorders to arteriosclerosis.

Recent studies have shown genetic influence on the metabolism of lipoproteins, on the excretion of sterols, and on the atherogenetic reaction of the arterial wall. This research, presently incomplete and in need of both confirmation and detailed investigation, will be fundamental to the identification of patients at high risk of arteriosclerosis as well as to the development of rational treatment.

A strong, general research program is needed in the pathogenesis of arteriosclerosis with emphasis on studies of lipoproteins and their interaction with the vessel wall. Recent progress in cellular research, enzyme studies, and collagen and mucopolysaccharide chemistry now allows sophisticated investigation of the tissue in the artery wall and its role in plaque formation. In addition, current population studies such as those in the Institute's Lipid Research Clinics and Specialized Centers of Research in Arteriosclerosis have identified a need for new and sophisticated investigations to clarify the role of nutrition in the development and treatment of arteriosclerosis.

Several clinical trials are currently underway to evaluate ways of preventing coronary heart disease. These efforts are aimed at investigating the potential benefits derived from controlling the risk factors of high blood lipids, high blood pressure, and smoking. Potentially useful drugs and surgical approaches are under study. Such important trials of potential preventive measures have both theoretical and practical value.

Arteriosclerosis takes years to become clinically evident. In the interval, the individual may appear to be in good health. Often the first evidence is catastrophic illness such as heart attack or stroke. Therefore, if we are to reach the patient before it is too late, efforts must be made to reach the patient in the community with the latest information through programs in health education, public motivation, and compliance with preventive or therapeutic regimens. (See section on Prevention, Control, and Education.)

ACTIONS

The Institute plans to:

1. Emphasize pathogenetic studies within existing research programs, centers of research, and lipid research clinics.

2. Stimulate development of sensitive, specific, invasive and non-invasive, convenient, and safe diagnostic techniques for use in determining arteriosclerotic changes in blood vessels.

3. Evaluate current techniques for diagnosis of hyperlipoproteinemia and other risk factors and encourage the development of better ones.

4. Establish colonies of suitable animal models with particular reference to nonhuman primates with arteriosclerotic or hypertensive disease for use in research on arteriosclerosis, hypertension, and cerebral vascular disease. Animal research will also be encouraged in genetics related to arteriosclerosis.

5. Expand current population studies in the Institute's Lipid Research Clinics, Specialized Centers of Research in Arteriosclerosis, and clinical applications and prevention programs to include in-depth genetic studies.

6. Encourage experts in psychology, sociology, and behavioral research to investigate the problems associated with health education and attitudes, motivation, and compliance as these relate to the prevention of arteriosclerosis, hypertension, or stroke and to the therapy and rehabilitation of patients with these diseases. (See section on Prevention, Control, and Education.)

7. Implement a Multiple Risk Factor Intervention Trial to determine whether, for men at above average risk of death from coronary heart disease (because of elevated serum cholesterol, elevated diastolic blood pressure, and cigarette smoking), a special intervention program will result in a significant reduction in mortality from coronary heart disease.

8. Continue an intervention study in high-risk subjects to test the effectiveness of lowering the concentration of lipids by selected means to reduce cardiovascular mortality and morbidity.

9. Provide for acquisition, analysis, and storage of data on the prevalence of different types of hyperlipoproteinemia, particularly in young age groups, with special emphasis on their relationship to diet and premature atherosclerosis.

10. Promote further clinical, laboratory, and epidemiologic studies of personal attributes and life styles such as nutrition, exercise, obesity, cigarette smoking, behavior, biochemical and hormonal patterns, and response to psychosocial stress and their relationship to the development of arteriosclerosis, coronary heart disease, stroke, and hypertension, particularly with respect to the onset of arteriosclerosis in the young and in women.

11. Expand current population studies and develop new epidemiologic studies of the role of environmental factors such as trace substances, water hardness, climate, geography, and occupational exposures in the pathogenesis of arteriosclerosis.

12. Implement the US-USSR cooperative study to define the prevalence of different types of hyperlipoproteinemia, their relationship to environmental factors, especially nutrition, as well as many broadly defined cardiovascular risk factors.

SCHEDULE

The costs of clinical trials now in progress will plateau in FY 75. Present programs related to the prevalence of lipid abnormalities and hypertension among children and young and middle-aged adults will be completed between FY 76 and FY 78. Program action will be continued or initiated in pathogenesis, instrumentation, epidemiology, genetics, nutrition, animal models, and behavioral studies.

2. HYPERTENSION

PROGRAM GOALS

High blood pressure is a leading cause of disease and death in the United States, particularly among the black population. It is a major risk factor in coronary heart disease. One of every six adults has some elevation of blood pressure. High blood pressure can be controlled, and we know that such control results in a reduced incidence of stroke and heart failure, kidney failure, and perhaps also a reduced incidence of heart attacks.

In more than 90 percent of the cases, the cause of the hypertension is unknown, and although the condition can be treated, it cannot be cured or prevented. Because of the large numbers of people affected by hypertension and its serious nature, it would be especially desirable to be able to prevent it; to accomplish this, increased emphasis is needed in fundamental research.

- The long-range goal in hypertension is to prevent it; the short-range goal is to optimize the utilization of effective treatment which currently exists.

RECENT PROGRESS

Research related to high blood pressure is a major effort within the Institute's program on heart and blood vessel diseases. The regulation of normal blood pressure is dependent upon striking a balance between a number of vasodilator and vasoconstrictor systems. Therefore, studies have been undertaken in each of these systems to identify their roles in hypertensive disease and also to define the interrelationships between them.

Kallikreins are enzymes which control the production of certain substances, kinins, which are potent endogenous vasodilators (agents that dilate blood vessels). Normal volunteers excrete on the average twice as much kallikrein in the urine as patients with essential hypertension. These patients appear to have reduced basal activity of the kallikrein-kinin system and also reduced responsiveness to physiologic stimuli.

The renin-angiotensin-aldosterone system is vasoconstrictor. During the past year radioimmunoassay procedures have been developed which are easier, quicker to perform, and very specific, sensitive, and reproducible. Normal levels of plasma renin activity (PRA) have been established and it has been shown that urinary and plasma kallikrein levels can be dissociated from PRA. It has also been demonstrated that a centrally acting antihypertensive drug, alphamethyldopa, is capable of lowering PRA.

The prostaglandins (PG) are endogenous unsaturated fatty acids with potent effects on blood vessels. A radioimmunoassay has been developed which makes it possible to measure very small amounts of these substances in the plasma or urine.

Catecholamines and the adrenergic nervous system have profound effects on blood pressure and renal function. Studies show that acute infusions or chronic administration of salt to normal humans cause an increase in a urinary substance, dopamine; a decrease in another substance, norephinephrine; and a decrease in a blood enzyme, dopamine β-hydroxylase. This enzyme plays a key role in the maintenance of the salt and water balance of the body.

Blood pressure, like most physiologic variables, is a periodic function. Studies on the classification, causes, and/or the treatment of hypertension are in progress, including a detailed study of the rhythm for blood pressure and the characterization of the circadian component. The ultimate objective is to define an optimal treatment for each patient with special reference to the abnormalities of controlling factors shown by that patient.

In the past year, unusual success has been achieved in the development of assays needed to carry out the complex biochemical studies needed for the investigation of factors relative to hypertension. Specialized laboratories are working on various assays of angiotensins, aldosterone, and prostaglandins to determine more fully the role of each in the pathogenesis and etiology of hypertension. In 1973, clinical tests were started of an agent which blocks the conversion

of Angiotensin I to Angiotensin II. Since Angiotensin I is inactive on blood vessels while Angiotensin II is an effective constrictor, it will be possible to measure the effect on blood pressure when one effector is eliminated. If this test proves to be as useful as anticipated, more laboratories will be encouraged to use it in their studies.

Epidemiological data will be forthcoming from the Hypertension Detection and Follow-up Program (HDFP) which began its operational phase in February 1973. Population data from 14 communities will become available to characterize prevalence of hypertension by a limited number of demographic, socioeconomic, and occupational characteristics. Follow-up of the 5,000 participants in the Regular Care Group will provide general population data on the progression of high blood pressure and its complications. An important component of the Hypertension Detection and Follow-up Program involves behavioral research as it relates to the identification of factors which enhance adherence to therapy or impede such adherence among individuals placed on antihypertensive drug management.

Data on high blood pressure are now available from six prospective epidemiological studies in populations which have had follow-up observations and blood pressure measurements over 4 to 18 years. Systematic analysis of these data is underway. Data from Puerto Rican, Israeli, Yugoslavian, Honolulu Japanese American, and Hiroshima Japanese populations are available to compare with the present 18-year follow-up data from Framingham.

An increasing number of projects deal with the role of stress in the genesis of hypertension. A pilot clinical trial of antihypertensive therapy in mild hypertension is being planned. This trial, jointly supported with the Veterans Administration (VA), is proposed for initiation in four VA hospitals.

An intensive study of the pharmacokinetic actions of antihypertensive drugs is underway. Combinations of available drugs are being tested in individual patients. It appears possible that therapy may soon be tailored to the functional aberrations found in an individual hypertensive subject.

FUTURE CHALLENGES

We do not know how beneficial treatment may be for mild forms of high blood pressure. Since an estimated 19 million people have mild hypertension, it is important that this information be developed. About 4 million people at any given time have hypertension of a degree known to be harmful. It can be controlled by medication with appropriate drugs. However, currently available drugs require close medical supervision and often have unpleasant side effects which make them difficult to use for long periods of time in asymptomatic individuals. We need to develop better pharmacologic agents without such side effects and without the need for meticulous, individually adjusted dosage.

Behavioral and motivational considerations similar to those mentioned under Arteriosclerosis are particularly important to the successful maintenance of antihypertensive therapy, since patients with high blood pressure seldom have characteristic symptoms until catastrophic complications occur. Rational treatment and prevention of hypertension will require an intensive investigation of its etiology and pathogenesis. While some current information about the formation and modulation of vasopressor polypeptides and related enzyme systems helps to explain pathogenetic mechanisms, we know little about etiology.

Dissemination of information about high blood pressure and the benefits of treatment represents a major challenge discussed in the section on Prevention, Control, and Education.

ACTIONS

The Institute plans to:

1. Emphasize research on the etiology and pathogenesis of hypertension, including its epidemiology, in many of the individual and specialized laboratories working on this problem.

2. Implement clinical trials of antihypertensive therapy in mild and labile hypertension.

3. Evaluate new pharmacologic approaches to the treatment of hypertension utilizing existing research centers and pharmacologic expertise, with emphasis on new drug formulations.

SCHEDULE

Present programs will continue to receive emphasis. The prevalence studies of hypertension in children will be completed as mentioned in the section on Arteriosclerosis. Continuing and new actions will increase somewhat in FY 75 and increase further by FY 79. Part of this increase is attributable to the proposed clinical trial of therapy for mild hypertension. Additional increases will occur in the pathogenesis and pharmacology of hypertension.

3. CEREBROVASCULAR DISEASE

PROGRAM GOALS

Cerebrovascular disease due to arteriosclerosis and especially due to hypertension is the basis for the great majority of strokes. An estimated 1.7 million adults in the United States have this disease, and of this number, about 200,000 persons will die of stroke each year. While the National Institute of Neurological Diseases and Stroke is primarily responsible for programs on those aspects of stroke that deal with brain injury and its consequences, the NHLI is responsible for programs on the cerebrovascular pathology that underlies the stroke.

- The goal of the NHLI program is to decrease the incidence of stroke through studies of the pathology and pathogenesis of cerebrovascular disease.

RECENT PROGRESS

A liaison Joint Council Subcommittee has been drawn from the Advisory Councils of the National Institute of Neurological Diseases and Stroke and the National Heart and Lung Institute, and other appropriate experts and Institute staffs for the purpose of coordinating and exchanging information on cerebrovascular diseases. During the past several years, this Subcommittee has served as a focus for information exchange, development of bibliographies, conferences and workshops and similar activities related to the National Program in cerebrovascular disease.

Currently within the National Program, only a small number of primarily human studies are concerned with the cerebral vasculature and its relationship to stroke. A few animal studies are concerned with the effects of hypertension on vessels, but do not relate primarily to the cerebral vessels. The experimental modeling of the vascular pathology of stroke in animals is a largely inactive research area for investigators in arteriosclerosis and has had only limited investigation in hypertensive models. There are no current studies of the combined effects of arteriosclerosis and hypertension on the cerebral blood vessels.

FUTURE CHALLENGES

To determine the etiology and prevention of stroke, we need to conduct animal studies of the effects of chronic arteriosclerosis and chronic hypertension on the arteries of the brain. Little knowledge is available as yet about chronic changes in animal models, particularly in nonhuman primates appropriate for neurological examination. The goals of these animal studies will be to elucidate, by methods not applicable to man, the vascular pathology that leads to stroke. Insofar as cerebrovascular disease is closely related to arteriosclerosis and hypertension, the future challenges discussed in the sections on Arteriosclerosis and Hypertension also apply to Cerebrovascular Disease.

ACTIONS

The Institute plans to:

1. Initiate studies in animals of the pathology of the lesions of chronic atherosclerosis and hypertension in the cerebrovascular arteries. Emphasis will be placed on those lesions that may contribute to ischemic stroke or arterial brain hemorrhage. The chronic and special animal resources referred to in the sections on Arteriosclerosis and Hypertension can be utilized with minor expansion or redirection for the study of cerebrovascular disease.

2. Continue prospective epidemiologic studies dealing with the identification of environmental factors and personal attributes which predispose to increased risks of stroke; maintain surveillance of stroke end-points in the clinical trials discussed in the sections on Arteriosclerosis and Hypertension.

SCHEDULE

The planned actions in animal studies and clinical research will gradually increase the current program effort in the cerebrovascular area through FY 79.

4. CORONARY HEART DISEASE

PROGRAM GOALS

Coronary heart disease is the major manifestation of atherosclerosis. It is the predominant form of heart disease in the adult American, causing 1.25 million heart attacks a year and responsible for chronic illness in 4 million Americans, 2.5 million below the age of 65.

Of the five major and well-established risk factors for coronary artery disease, namely age, male sex, high blood lipids, high blood pressure and cigarette smoking, the latter three can be modified, and two of these are known to result in reduced cardiovascular risk when deliberately decreased. Cessation of cigarette smoking will decrease the enhanced risk of heart attacks among smokers, and reduction of moderate or severe hypertension reduces stroke and some other complications of high blood pressure. Its effect on heart attack or sudden cardiac death is unknown but may be appreciable. The Institute has implemented three large-scale trials to evaluate the cardiovascular effects of risk factor modification. These are described in the previous sections on Arteriosclerosis and Hypertension.

A research program focused on patients with acute heart attacks has developed extensive information about pathophysiology; prognostic factors; pharmacological, surgical, and circulatory assist therapy; and techniques and instruments for conducting research in the acutely ill patient. These developments can now be built upon and more broadly used.

- A primary goal of the program is to develop information that will lead to improved diagnosis, prevention, therapy, rehabilitation, and understanding of the mechanisms resulting in symptomatic coronary disease.

Coronary artery bypass surgery has been developed to supplement medical management of coronary heart disease, particularly in the case of angina pectoris. This technique uses a blood vessel graft to bypass a narrowed or occluded segment of a coronary artery. Over 25,000 such operations are done annually in the United States with hospitalization costs in excess of $5,000 for each operation.

- A second goal is to establish the indications for and the effects of coronary artery surgery in the treatment of various forms of coronary heart disease.

Each year about 400,000 deaths from coronary heart disease occur before hospitalization, half of these almost instantaneously or unwitnessed. Over three-quarters of these victims have known heart disease or high blood pressure before their sudden deaths, but in the rest, sudden cardiac death is the first evidence of heart disease.

- A third goal is to develop and assess emergency medical care methods for heart attack victims and to develop and evaluate prophylactic treatment with drugs to prevent sudden cardiac death.

Following heart attack or other manifestation of heart disease, tens of thousands of Americans annually are left with substantial impairment of their ability and freedom to function and to contribute fully to society.

- A fourth major goal of the program is to assess the needs and opportunities for cardiac rehabilitation with respect to physical, physiological, and societal factors to prevent disability and to bring back into the mainstream of life those who have suffered cardiovascular disease.

In addition to topics identified under Coronary Heart Disease, closely related work is included in the sections on Arteriosclerosis, Arrhythmias, Heart Failure and Shock, and in the section on Prevention, Control, and Education.

RECENT PROGRESS

In 1972 and 1973, the Institute implemented three large-scale clinical trials, as described in the sections on Arteriosclerosis and Hypertension, directed toward evaluating the cardiovascular effects of risk factor modification. After two to five years of planning, the Hypertension Detection and Follow-Up Program, Lipid Research Clinic, and Multiple Risk Factor Intervention trials have begun patient recruitment. Within this decade, we should know the impact of lowering lipids on heart attack in certain types of lipid disorders, the impact of controlling hypertension on heart attack, as well as the impact of controlling simultaneously the three major risk factors.

Plans for Specialized Centers to conduct research on the various manifestations of coronary heart disease have been developed. Phase I of the Collaborative National Study on Coronary Artery Surgery is completed. The US-USSR Cooperative Study on Management of Ischemic Heart Disease is moving forward on schedule. The results of present studies on mechanisms and factors precipitating acute cardiovascular events and their prodromata are being evaluated. Pilot testing of antiarrhythmic drugs to be given to patients following hospitalization for acute myocardial infarction is progressing satisfactorily.

Studies for early administration of prophylactic antiarrhythmic drugs in the emergency care settings have begun but are proceeding slowly. A task force has been established to assess the needs and opportunities for the physiological, psychological, and societal rehabilitation of patients with cardiovascular disease.

Scientific research in the past has resulted in the current treatment of heart attack, specifically relief of pain and prevention or reversal of rhythm disturbances which can be lethal. Recent investigations (more fully described in the section on Heart Failure and Shock) have shown that the size of the infarct (the amount of dead heart muscle) is directly related to death or disability from a heart attack. Studies are currently underway to develop better ways to assess infarct size as well as to assess therapies for limiting the size of infarcts. For example, for many years, physicians have administered oxygen to patients with heart attack, although firm scientific evidence for its usefulness has not existed. Recent animal experiments show that inhalation of oxygen decreases the extent of damage to heart muscle. This suggests that there is indeed rationale for its continued use in patients. The use of a pump to assist the heart in patients with heart attack has been shown to relieve pain, and if applied early in the course of the attack, limits the amount of heart muscle destroyed. In combination with certain drugs, the effect is even more striking.

FUTURE CHALLENGES

The emphasis in patient-oriented research must shift from its current focus upon acute heart attack to the inclusion of other important aspects of coronary heart disease--angina pectoris, heart failure, arrhythmias, and sudden death. Attention must be paid to further development and evaluation of therapy, rehabilitation, and measurement techniques. The fundamental question of why chronic coronary artery disease is finally manifested as acute heart disease--heart attack or sudden death--must be answered. These research areas have been emphasized by the National Heart and Lung Advisory Council. The study of susceptible patients requires specialized facilities that are complex, expensive, and staffed with personnel who are available for emergencies. Importantly, such specialized cardiological facilities will be very useful for research on other forms of heart disease as well.

It is widely recognized that coronary artery surgery brings relief of symptoms for a majority of patients with severe angina pectoris. However, the benefits and side effects, the value compared to conventional drug therapy, and the effects upon lifespan and quality of life require further research.

Recent studies have shown that the final step in sudden cardiac death is usually ventricular fibrillation, which is largely preventable during hospitalization by drugs given intravenously. Thus, finding drugs to prevent ventricular fibrillation in high risk patients is an important research task, and agents must be found that can be used immediately upon the development of heart attack symptoms.

The high frequency of out-of-hospital deaths and the favorable experience with improved systems of emergency cardiac care underscore the need for further development of emergency-related techniques and resources for use in cardiac patients. A strengthened scientific basis for rehabilitation programs and a more comprehensive scope of action for these programs are needed. Development and testing of new hypotheses and methods are critical to continued clinical and fundamental research into the cause, diagnosis, and treatment of coronary heart disease.

ACTIONS

The Institute plans to:

1. Establish approximately 12 specialized units to conduct research upon the various manifestations of coronary heart disease. Comprehensive clinical investigation will be supported by related, fundamental laboratory studies.

2. Establish a collaborative national program to determine the indications for and the long-term effects of coronary artery surgery in the management of coronary heart disease. Randomized studies will be utilized in patients with sharply defined clinical conditions and coronary arterial involvement. A registry will be used to follow patients in whom the indications for surgery or exclusively medical treatment seem sufficiently clear that randomized allocation would be improper, but in whom follow-up clinical data are important for assessing the validity of present clinical judgments.

3. Implement the US-USSR cooperative study on the management of ischemic heart disease by medical and surgical techniques.

4. Promote studies to elucidate the mechanisms and factors which precipitate acute coronary events and to determine the characteristics of individuals at highest risk for these events.

5. Promote studies on the prodromata of acute coronary events and of patients' reactions and coping behavior in this setting with a view toward earlier diagnosis and treatment.

6. Develop and test techniques of emergency cardiovascular diagnosis and therapy suitable for incorporation into emergency medical care systems.

7. Design, pilot test, and subsequently implement large-scale trials of chronically administered antiarrhythmic drugs in patients at high risk for sudden cardiac death.

8. Implement the US-USSR cooperative study on the prevention of sudden cardiac death.

9. Design, pilot test, and subsequently implement large-scale trials of the early administration of prophylactic antiarrhythmic drugs immediately upon the development of heart attack symptoms.

10. Assess the needs and opportunities for cardiac rehabilitation in terms of physical, psychological, and societal factors, and implement appropriate programs of research.

SCHEDULE

The present long-term study of lipid-lowering drugs aimed at preventing recurrence of heart attack or death from coronary heart disease (the "Coronary Drug Study") is being completed in FY 74 and will be terminated by FY 75. The Myocardial Infarction Research Units, which have focused upon heart attacks, will be discontinued by FY 75. Continuing and new actions in coronary heart disease will emphasize manifestations other than heart attack, particularly angina pectoris and sudden cardiac death. In part, this will be accomplished through the development of specialized units. The emphasis will shift toward electrophysiological and surgical investigations, with specific attention to prevention of acute events.

5. PERIPHERAL VASCULAR DISEASES

PROGRAM GOALS

Peripheral vascular diseases are the cause of considerable suffering and disability. Surgeons have developed techniques to replace diseased peripheral artery segments with vascular or prosthetic grafts. Otherwise, peripheral arterial disease has been the focus of only a limited research effort, and peripheral venous disease and disorders of the lymphatics have received even less emphasis.

- The goals of this program are to improve diagnosis, therapy, and rehabilitation, and to improve understanding of the mechanisms causing peripheral arterial, venous, and lymphatic diseases.

RECENT PROGRESS

Some epidemiological data on the prevalence, incidence, and potentiality of risk factors are being obtained from prospective population studies. The bulk of developments related to Peripheral Vascular Diseases is described in the section on Arteriosclerosis.

FUTURE CHALLENGES

Methods must be developed for diagnosing peripheral vascular diseases before they reach an advanced state, for more effective medical management, and for extending surgical therapy to small vessels. Understanding the basic cause of the diseases is most important and will require study of the role of neural control of vascular tone, mechanism of action of smooth muscle, pathogenesis of peripheral atherosclerosis, and the importance and significance of risk factors.

ACTIONS

The Institute plans to:

1. Encourage clinical, laboratory, and epidemiological research into the causes, diagnosis, and treatment of diseases of the peripheral arteries, veins, and lymphatics.

2. Implement related programs described in the section on Arteriosclerosis, and the programs on noninvasive instrumentation discussed in the section on Bleeding and Clotting Disorders under Blood Diseases and Blood Resources.

SCHEDULE

Continuing and new Actions in peripheral vascular diseases will emphasize clinical and basic investigation. Emphasis will be on diagnostic techniques for small vessels, and the relation of physiology and pathophysiology to clinical manifestations of disease. Multidisciplinary approaches will be emphasized as well as specific approaches.

6. ARRHYTHMIAS

PROGRAM GOALS

Important new concepts are developing about the correlation of electrical signals from the heart and the extent, severity, and prognosis of heart disease. Information is being accumulated about the different causations of arrhythmias and their differential responses to drug therapy. Most of the drugs currently effective in the treatment and control of arrhythmias have side effects which limit their applicability.

- A major goal of the program is to develop methods for the prevention of arrhythmias which specifically cause sudden cardiac death.

Identification of arrhythmias that carry a high risk of sudden cardiac death is fundamental to preventive measures and has been emphasized by the National Heart and Lung Advisory Council. The analysis of spontaneous rhythms and the influence of drugs must be assessed by quantitative analysis of extensive electrocardiographic tape recordings. Substantial progress has been made toward performing this task automatically, rapidly, and quantitatively by computer.

Arrhythmias and other electrical disturbances of the heart cause important symptoms and aggravate many forms of heart disease.

- Another goal of the program is to improve currently available methods for prevention, diagnosis, and management of arrhythmias and other electrical disturbances of the heart.

RECENT PROGRESS

Clinical studies are in progress to identify chronic or intermittent disturbances of rhythm, and several projects are primarily directed at the electrophysiology and therapy of rhythm disturbances associated with inadequate blood supply to the heart. A collaborative study is being developed to describe significant arrhythmias in specific groups of patients and their modification by drug therapy. Improved automated arrhythmia analysis of electrocardiographic records is being achieved.

A previously undefined syndrome of potentially major clinical importance has recently been described. This new syndrome is called the Primary Ventricular Fibrillation Syndrome or the Instantaneous Death Syndrome. Clinically, those patients fortunate enough to be resuscitated following their sudden collapse exhibit disturbance of heart rhythm, absence of recent or evolving myocardial infarction, chronic coronary artery disease, and a very high incidence of sudden death (at 30 percent per year) subsequent to resuscitation. Pathologically, from medical examiners' series, the syndrome is characterized by severe chronic coronary artery disease, absence of recent coronary artery lesions, and no evidence of recent myocardial necrosis.

This syndrome, which may comprise up to 50 percent of all cases of sudden cardiac death, can be differentiated from other cases of sudden cardiac death which have been characterized clinically by ventricular fibrillation, a high incidence of premonitory symptoms, recent or evolving acute myocardial infarction, and a lower occurrence of subsequent sudden death (at 2 percent per year). The recognition of this new syndrome presents a challenge for preventing premature death from coronary artery disease.

FUTURE CHALLENGES

A better understanding of the electrical behavior of ischemic heart muscle is essential to the prevention of sudden cardiac death. Several drugs which are effective agents in the setting of the coronary care unit need to be evaluated for benefits and side effects as prophylactic agents outside the hospital in patients suspected of having myocardial infarction. Particular attention needs to be paid to the effect of heart rate upon automaticity and rhythm disturbances as well as upon the work load and consequent potential damage to the heart. Antiarrhythmic drugs, which can be taken orally over long periods of time, and which have shown promise in limited clinical trials, need to be evaluated in larger-scale trials. Fundamental to all these clinical studies is the development of systems for quantifying electrocardiographic rhythm signals automatically and rapidly. In addition to the efforts focused upon ventricular fibrillation and the prevention of sudden cardiac death, disturbances of the conduction system of the heart, as well as other important rhythm disturbances, must be managed more effectively. Closely related topics are also discussed under the section on Coronary Heart Disease.

ACTIONS

The Institute plans to:

1. Expand current programs for the prevention of arrhythmias causing sudden cardiac death, focusing particularly upon the electrophysiology and therapy of rhythm disturbances associated with inadequate blood supply to heart muscle and upon clinical studies to identify chronic or intermittent disturbances of heart rhythm which indicate an increased risk for sudden death.

2. Augment the development of automated, quantitative techniques for analyzing electrocardiographic rhythm signals to facilitate clinical investigation of arrhythmias.

SCHEDULE

It is anticipated that the current major emphasis on descriptive aspects of conduction disturbances will be somewhat diminished. Continuing and new Actions related to arrhythmias will emphasize those fundamental to understanding sudden cardiac death. There will be an overall expansion of program activity with a peak in currently projected programs in FY 78 and FY 79, and subsequent levelling off of activity by FY 80.

7. HEART FAILURE AND SHOCK

PROGRAM GOALS

Heart failure and shock may be the end result of many different diseases. The National Heart and Lung Advisory Council has given priority to studies of heart failure. In a heart attack, blood supply to a part of the heart muscle becomes so severely reduced that the muscle undergoes irreversible damage. It can no longer contract or pump and is ultimately replaced by a scar. The amount of irreversibly damaged muscle is not predetermined at the onset of the heart attack; there is a zone which is in jeopardy but has not yet progressed to the point of no return. Current research has identified several promising means for protecting this zone of potentially reversible damage and for promoting its recovery. Some of these approaches are being investigated in initial clinical feasibility trials; other promising techniques are being tested in animal studies.

- A major goal is to minimize heart failure associated with and following heart attack by enhancing the survival of damaged heart muscle.

Methods to quantify the amount of heart muscle which is inadequately perfused or which has undergone irreversible damage are crucial to the evaluation of therapeutic interventions. Recently, several such

methods have shown promise. They may make it possible to test new approaches more economically and in fewer patients than is now required for evaluation by gross clinical criteria.

- A second goal is to develop more satisfactory means of quantifying the extent of heart muscle which is inadequately perfused with arterial blood or which has undergone irreversible damage.

Other aspects of the diagnosis, etiology, therapy, and prevention of heart failure and shock warrant emphasis. These include research on improving the pumping function of heart muscle, as well as understanding and treating the disturbances of the regulation of peripheral blood vessels, the related endocrine functions of the body, and the functioning of the kidney.

- A third goal of the program is to improve understanding and management of heart failure and shock due to cardiovascular causes.

RECENT PROGRESS

The biochemical and physiological studies fundamental to the survival of heart muscle and to the development of methods to prevent heart muscle damage are continuing. Pilot studies with a variety of therapeutic agents are underway and some show considerable therapeutic promise. Examples of such agents are cited in the section on Coronary Heart Disease. Progress is also being made in radioisotopic quantification of heart muscle which is underperfused or damaged.

FUTURE CHALLENGES

Current therapy to enhance the survival of ischemic heart muscle must be evaluated on a larger scale by more definitive clinical studies than those now underway. The effects upon infarct size must be quantified and survival assessed. Ischemic heart muscle must be studied at the cellular and subcellular levels, in an effort to develop more effective therapy.

The techniques for quantifying the degree of heart muscle damage must be validated. Subsequent use of the best techniques would minimize the number of patients needed for evaluation of new modes of therapy. Electrocardiographic, enzymatic, and radioisotope techniques show promise.

Studies of heart failure and shock need to be expanded to include other organ systems. Thus, as the National Heart and Lung Advisory Council has recommended, the dynamics and the neural and endocrine control of the circulation must be studied in the periphery as well as in the heart, kidney, and other organs.

ACTIONS

The Institute plans to:

1. Enlarge biochemical and physiological studies of the fundamental processes associated with heart muscle survival both in laboratory and clinical studies. Based upon these studies, develop methods for minimizing the extent of heart muscle damage in a heart attack.

2. Establish clinical studies, contingent upon success of current pilot studies, to assess the therapeutic efficacy of promising techniques for minimizing the extent of heart muscle damage.

3. Expand the program for quantifying the extent of heart muscle which is inadequately perfused or which has undergone irreversible damage.

4. Implement the US-USSR cooperative program on myocardial metabolism.

SCHEDULE

Continuing and new Actions related to cardiac failure and shock will emphasize the pathophysiology of ischemic myocardium and methods of quantifying this condition, as well as directing attention to systemic responses to heart failure and shock. Clinical trials will be ready for phase-in in FY 75 and FY 76; a number of promising techniques have progressed to a stage where they are ready for clinical evaluation on a moderate scale. These new efforts were initiated in FY 74. The program will peak in FY 79, and begin to level off by FY 80.

8. CONGENITAL AND RHEUMATIC HEART DISEASES

PROGRAM GOALS

Congenital and rheumatic heart diseases are important disorders of childhood, and may form the basis for considerable impairment of the quality of life of the patient surviving into adulthood.

The earliest surgical successes in the treatment of heart diseases were in the correction or palliation of congenital heart disease. These successes are being expanded in the development of diagnostic and surgical techniques applicable to the newborn. Important insights have also been gained into the development of the cardiovascular system. However, in most cases, science still does not know what makes the heart develop abnormally before a baby is born.

- The major goals of the program are to understand better the causes of congenital heart disease, to improve diagnosis and therapy, and to rehabilitate patients with congenital heart disease, particularly the newborn.

Rheumatic heart disease is an immunological disturbance that frequently occurs years after initial rheumatic fever and prior streptococcal infection. It can not only shorten life, but also seriously impair the quality of the patient's life. Improved understanding and control of immunological problems could thus be important in the identification of susceptibility and the prevention of rheumatic heart disease, as well as in the success of cardiac transplants and in the prevention or treatment of cardiomyopathy and possibly other forms of heart disease.

- Another important goal is to attain a better understanding of the immunological problems associated with heart diseases.

Closely related programs are discussed in the section on Prevention, Control, and Education, and deal with the management of congenital heart diseases in the newborn.

RECENT PROGRESS

The Institute has maintained a continuing long-term effort focused upon all facets of the problems of congenital and rheumatic heart disease, resulting in a steady improvement in the clinical management of these patients. Extremely delicate operations that were inconceivable a few decades ago are now performed routinely in most of the major medical centers. It is now possible to perform very complex repair of the heart even in young infants.

FUTURE CHALLENGES

Essential to the prevention of congenital heart disease is a better understanding of the normal development of the cardiovascular system and the causes of abnormal development. The National Heart and Lung Advisory Council has recommended that the Institute conduct an "intensive interdisciplinary study of all aspects of the etiology and pathophysiology of congenital heart disease and the neonatal cardiovascular system." The roles of maternal infection and toxic exposures during pregnancy are particularly relevant. The emphasis on diagnosis, therapy, and rehabilitation of congenital heart disease patients must increasingly involve the newborn, as well as school age children. Particular attention must be paid to measures that will "assure the first few hours of life." Research challenges in the management of congenital heart diseases in the newborn are closely related to programs discussed further in the section on Prevention, Control, and Education.

The roles and nature of immune mechanisms as they relate to the heart need to be better understood. Therapy for the suppression of harmful immunological responses must be developed and evaluated.

Both clinical and fundamental research on causes, diagnosis, and therapy of congenital heart disease, rheumatic fever, and rheumatic heart disease must be continued with periodic updating of approaches.

ACTIONS

The Institute plans to:

1. Establish Specialized Centers of Research in Congenital Heart Disease at two to four locations in FY 76. The research in these Centers will emphasize such topics as cardiovascular development and improved diagnostic techniques and therapy, particularly in the newborn.

2. Establish a targeted effort to study immunological problems in heart disease and their management, specifically in relation to rheumatic heart disease, cardiac transplantation, and cardiomyopathies.

3. Implement the US-USSR cooperative study on congenital heart disease.

SCHEDULE

There will be a diminished emphasis on the hemodynamic and surgical aspects of these diseases in older children and adults. The continuing and new actions will emphasize the causes of both congenital and rheumatic heart diseases. In coordination with the National Institute of Child Health and Human Development, the National Heart and Lung Institute will give special attention to the role of infections, drugs, and other toxic exposures during pregnancy in congenital heart disease. For congenital heart disease, there will be an increasing clinical emphasis on the neonatal period.

9. CARDIOMYOPATHY AND INFECTIONS OF THE HEART

PROGRAM GOALS

Cardiomyopathy and infections of the heart, which are diseases of the heart muscle and its lining, cause enlargement of the heart, heart failure, irregularities of heart rhythms, and occasionally sudden death. The prevalence of these diseases, caused by a variety of factors, is unknown.

- The goals of the program are to prevent, diagnose, and treat the various cardiomyopathies and infections of the heart, with particular emphasis on improved understanding of their causes.

RECENT PROGRESS

New ways of studying these diseases have been developed. Cardiomyopathies and infections of the heart are being recognized with increasing frequency. The importance of toxic substances, viral infections, and immunological phenomena is widely recognized, although a number of causes remain unknown. Accordingly, the National Program is giving priority to identification of the etiologies of cardiomyopathy. The advent of antibiotics has substantially diminished heart disease caused by bacterial infections. However, new problems have arisen, such as infections on prosthetic heart valves.

FUTURE CHALLENGES

There is particular need to understand the causes of cardiomyopathies and myocarditis. Cellular and subcellular biochemical and immunological studies offer opportunities for improving our understanding of these problems. The roles of toxic substances, including drugs and alcohol, and of viral infections and genetic disorders need to be investigated. Better diagnostic and therapeutic approaches to these diseases must be developed. Since these diseases stem from a variety of causes, research efforts need to be broadly based and involve multiple disciplines.

ACTIONS

The Institute plans to:

1. Focus attention on studies of the etiologies of cardiomyopathies and infections of the heart, emphasizing epidemiological methods, viral and immunological research, the development and utilization of animal models, and the determinations of mechanisms of myocardial damage by application of biochemical, physiological, physical, and pharmacological techniques. (See also Congenital and Rheumatic Heart Diseases, Action #2 on immunological problems.)

SCHEDULE

Continuing and new actions, with initial emphasis on causation, will permit increase in activity as this unresearched field is developed, with progressive increases in funding through FY 80.

10. CIRCULATORY ASSISTANCE

PROGRAM GOALS

Present and foreseeable techniques of general and pharmacological management of acute and chronic cardiac insufficiency and shock still leave a substantial fraction of patients with compromised or fatally impaired heart function. By mechanical supportive means, it is possible to substitute some of the pumping function of the heart and to relieve its work load. Presently, such techniques are possible briefly in man and for longer periods in the experimental animal.

- A major goal of the program is to develop and assess therapeutically effective, safe, and reliable cardiac assist and total replacement heart devices for supporting or taking over the work load of the heart.

Methods for assessing and quantifying the degree of circulatory impairment are also necessary to evaluate patients with all forms of suspect or known heart disease and particularly for patients with heart failure and shock.

- A second goal is to develop the instrumentation and techniques for the assessment of cardiovascular performance.

RECENT PROGRESS

Partial and totally implantable left ventricular assist devices may be significant in the future in terms of correcting acute and chronic cardiac insufficiency. In recent experiments, a left ventricular assist device has performed successfully in vivo in calves. In ten acute implantations, excellent results were obtained in terms of cardiac output, heart rate, and blood pressure.

Left ventricular assist with intra-aortic balloon counterpulsation was introduced into clinical studies about a decade ago. Studies showed that this form of mechanical assist could temporarily reverse shock in subjects refractory to all forms of medical therapy, permitting additional diagnostic and therapeutic procedures. Additionally, in a small group of patients with severe refractory shock, an occasional life could be salvaged. However, the overall impact of this form of therapy in patients with acute myocardial infarction remained to be determined, especially in relation to the morbidity and mortality in those patients less critically ill. Recent patient studies have now shown a definite reduction of infarct size associated with the use of this mechanical device. This reduction of infarct size, which previously could only be demonstrated in animal studies, may represent a promising method to decrease subsequent patient morbidity and mortality.

FUTURE CHALLENGES

Mechanical techniques for augmenting or substituting for the performance of the heart must be expanded to encompass emergency temporary devices for short-term management, extracorporeal assist pumps for intermediate periods of use, long-term implanted heart assist devices, and total cardiac replacements. An associated opportunity and need exist for research on the physiology of assisted circulation, as well as on the development of the requisite components of the systems--compatible biomaterials, pumps, actuators, energy transforming devices, implantable energy systems, transcutaneous transmission of energy, and the control system for the devices.

Plans for the future include chronic in vivo assist experiments in calves, followed potentially by clinical application in man for short-term left-heart bypass support. Eventually, longer-term implantation in man for the purpose of supporting or totally replacing a weakened heart may result.

These types of studies with mechanical circulatory assist are very promising, and further work is now clearly indicated. Smaller infarct size has been associated with a better patient prognosis, but the effect of reducing infarct size on prognosis has not been definitely proven. Finally, the subgroup of acute myocardial infarction patients who might benefit most from this relatively invasive type of procedure must be determined before this intervention is widely recommended.

ACTIONS

The Institute plans to:

1. Continue the research, development, and assessment of emergency temporary, circulatory support devices directed at short-term management of heart failure and shock to stabilize the clinical condition and permit its reversal.

2. Expand the research, development, and assessment of implantable heart assist devices capable of taking over a significant fraction of the work of the heart for extended periods of time.

3. Undertake research, development, and assessment of external heart assist devices capable of taking over a significant fraction of the work of the heart, and requiring minimal surgery for connection and removal.

4. Expand research, development, and assessment of implantable heart replacement devices for permanent implantation.

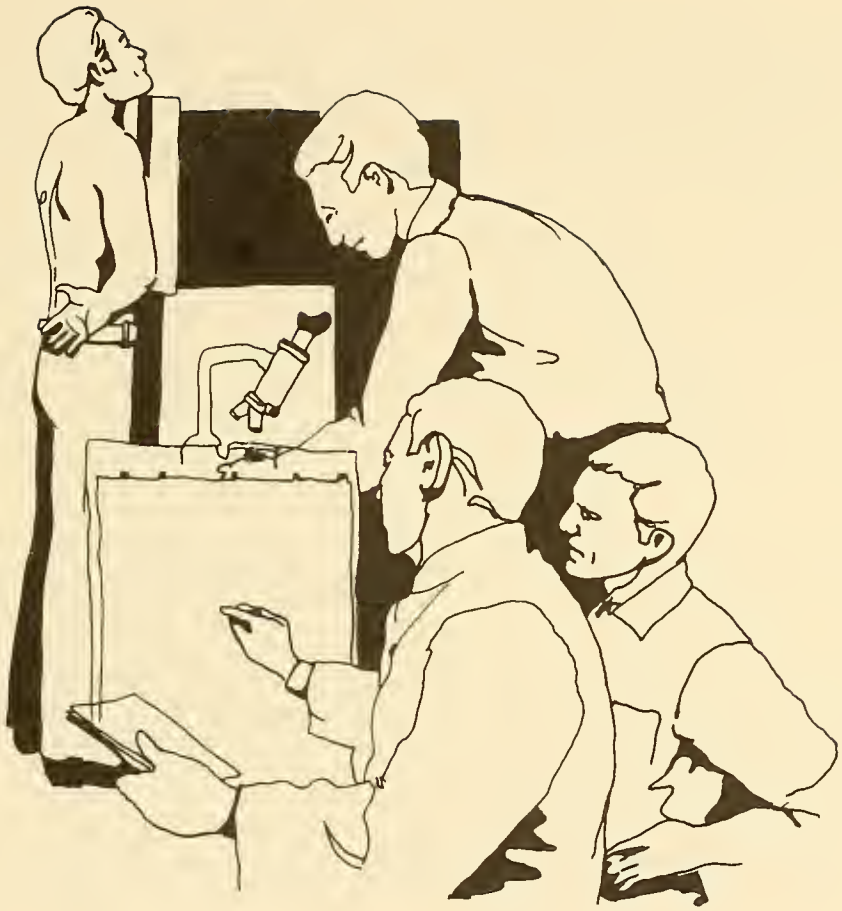
5. Expand research and development upon circulatory assist and artificial heart systems, including the development of compatible biomaterials, appropriate pumps, actuators, energy transforming devices, implantable energy systems, transcutaneous transmission of energy, and control systems for the devices.

6. Expand research and development of noninvasive and invasive instruments and techniques for the assessment of cardiovascular performance.

SCHEDULE

Present programs in the development of circulatory assist devices will continue. An assessment will be made of long-range goals to include the relative needs and opportunities for the development of devices which offer substantial clinical benefit, yet fall short of the most ambitious goals of totally implantable and permanently energized long-term cardiac assist or replacement.

The selective termination of targeted activities as their objectives are met will be outweighed by the need for larger-scale reliability and performance tests prior to and with the advent of substantial long-term clinical implants.



LUNG DISEASES

The National Heart, Blood Vessel, Lung, and Blood Act encourages the Institute to place greater emphasis on lung diseases in the National Program.

Lung Diseases covered by the Program account for an estimated 150,000 deaths each year in the United States, cause 60 million days lost from work, 40 million days of bed-restricted activity, and cost the economy about $6 billion a year in lost productivity and wages and medical care costs.

In 1972, the National Heart and Lung Institute convened a task force to assist in identifying high-priority problems and approaches for immediate and long-range plans to expand the attack on lung diseases in our country. In this effort, 188 scientists assessed the magnitude of respiratory disease problems in the U.S., reviewed available knowledge on the causes of respiratory diseases and the methods for diagnosis and treatment; pointed to disparities between current efforts and needs in controlling these diseases; and recommended ways to strengthen present research programs.

The task force report became a primary resource document for the Lung Diseases Panel, convened in the fall of 1972 in response to the legislation. The recommendations of this Panel were reviewed by the Institute, the National Heart and Lung Advisory Council, and the Interagency Technical Committee, and formed the basis for developing the Institute's expanded program on lung diseases, as well as for developing the plans for coordination of the overall National Program in Lung Diseases.

The initial lung program has been reviewed and updated by the Institute during the past eight months. The updated National Program is presented here and represents an assessment and orderly expansion of NHLI activities in respiratory diseases. The Program continues to be responsive to the Legislative Act, which encourages special attention to childhood diseases and chronic lung diseases, including the establishment of National Research and Demonstration Centers. The Institute's program, which addresses immediate as well as long-range objectives, centers on three specific approaches of comparable importance and urgency:

- Research on the structure and function of the lung in order to gain fundamental information which will improve our understanding of important factors in the promotion of health and the prevention and treatment of lung diseases.

- Expansion and development of our knowledge base on specific diseases which constitute national health problems, but which represent areas where current information is insufficient to provide immediate solutions.

- Application of available technical resources to solve specific problems whose solutions are expected to pay immediate dividends in improving the health of our nation.

The updated program goals, recent progress, future challenges, actions, and schedules for implementation are discussed below for each program area:

1. Structure and Function of the Lung
2. Pediatric Pulmonary Diseases
3. Emphysema and Chronic Bronchitis
4. Fibrotic and Immunologic Lung Diseases
5. Respiratory Failure
6. Pulmonary Vascular Diseases
7. Inhalation Diseases
8. Respiratory Assistance.

The first five program areas are continuations of those outlined in the initial Plan. The last three areas have been added this year and given increased emphasis in the updated lung diseases program. The Institute's revised Plan incorporates most of the Actions set forth in the initial Plan without change or only slight revision. Seven new research Actions have been added this year for the three new program areas. The respiratory diseases addressed by the Institute do not include cancer of the lung, which is the concern of the National Cancer Institute, nor upper respiratory infections or pulmonary tuberculosis, which are the concern of the National Institute of Allergy and Infectious Diseases, and, in certain cases, of the Center for Disease Control.

1. STRUCTURE AND FUNCTION OF THE LUNG

PROGRAM GOALS

Our current capability to deal with the problems of lung disease in the United States is severely limited by our lack of fundamental knowledge about the lung. This knowledge must be gained before truly definitive preventive and therapeutic measures can be designed. Current remedies are not only very costly but are also only temporary, stopgap techniques which need to be replaced by more specific and longer-term methods yet to be discovered through research. Thus, the most important priority now in the Institute's lung diseases program is to expand research on the lung and its biology in order to identify factors critical to the health of the lungs. Recent progress in basic scientific disciplines, such as molecular biology, biochemistry, immunology, and ultrastructural anatomy offer new opportunities for making major advances toward combating emphysema, chronic bronchitis, pulmonary fibrosis, asthma, pediatric pulmonary diseases, respiratory failure, pulmonary vascular diseases, and inhalation diseases.

- While it is essential to first focus studies on the cellular biology of the normal lung, the ultimate goals of the program are to increase understanding of the disease processes and develop effective methods for prevention, diagnosis, and therapy of lung diseases.

RECENT PROGRESS

Recently, a major step has been taken toward an understanding of lung disease mechanisms. The lung--an organ with numerous functions that include gas exchange, defense against diseases, and removal of inhaled substances such as dust--is made up of about 40 different types of cells. Recent progress in studies at the cellular level has contributed to understanding relationships between lung structure and function. Studies have advanced to the point that it should be possible to describe the multiple functions of the various types of lung cells in terms of cellular and biochemical changes associated with different respiratory diseases.

However, before such abnormalities can be understood, it is necessary to have a firmer knowledge of normal lung cell structure and function. This is a difficult research task because of the multifunctional nature of the lung and because of the various roles performed by different lung cells. Unless the different types of lung cells can be isolated and studied separately, the changes associated with various disease states will be impossible to pinpoint. Recently, an enzymatic procedure has been developed for dispersing lung tissue into separate viable cells, thereby providing an opportunity to isolate and culture individual cell populations from whole lung tissue.

The major advantage of using cell culture techniques is that large quantities of a single cell type can be accumulated and readily used in experiments. Once techniques are developed to culture single cell types, the specialized requirements for cell growth may be examined, and ultimately a comparison made of cells grown from normal individuals and those from individuals with specific lung diseases.

FUTURE CHALLENGES

The next several years of research activity will provide information relating structural and biochemical characteristics of individual lung cells. As this information develops, investigations into the molecular basis of lung disease should be possible. This is an essential step toward effective prevention and treatment.

Specific opportunities and needs for the future include studies of the quantities, composition, and mechanisms of development of various components in normal lung tissues, and their chemical precursors and possible variations with age, sex, and environmental influences. Structural proteins, lipids, and hormones may be involved in diffuse pulmonary fibrosis and in various types of obstructive disease of the airways. The *in vivo* balance and interaction among proteolytic enzymes and their potential for altering the connective tissue in the lungs need to be elucidated. The turnover rates of lung cells and alterations in these rates with disease require further study.

Failure of the lung's defense mechanisms may play an important part in disease processes. The structure, synthesis, and physicochemical properties of bronchial mucus, one of these defense mechanisms, need to be investigated. The cilia in the bronchial tree are another vital defense mechanism. Information on their structure and function is crucial to understanding lung clearance and host defense.

Some classical areas of pulmonary physiology require continued study and correlation with new knowledge of cellular biology, structure, and function. Physiologic studies will continue to develop information on the mechanical properties of the lungs and the pulmonary blood vessels, and the coupling of mechanical events to the neurophysiological regulation of ventilation.

ACTIONS

The Institute plans to:

1. Encourage investigator-initiated research in metabolism, cellular biology, and defense mechanisms of the lung. This will be supplemented as needed by targeted research addressed to topics not adequately covered by investigator-initiated research.

2. Develop multidisciplinary approaches, such as program projects or Specialized Centers of Research, in the area of normal lung structure and function. In addition, we will initiate new types of targeted programs for collaboration and exchange of information between basic scientists such as biochemists, immunologists, and cell biologists, who are not yet focusing on the lung, and pulmonary specialists who need to develop information in basic science areas.

3. Seek new information on the structural components of the lung. Encourage studies on the alterations in proteins and cells associated with dissolution of lung tissue as a consequence of injury.

SCHEDULE

New research programs in lung cell separation and culture are being encouraged. A program on the separation and characterization of lung elastin is being developed. Synthetic inhibitors for the enzyme elastase will be prepared and distributed to the research community. A workshop will be sponsored to encourage research on metabolic functions of the lung. Programs which are not included in the planned priority actions relating to structure and function of the lung will not be further developed. Continuing and new actions in pulmonary structure and function will be divided between multidisciplinary and specific approaches with gradually increasing activity through FY 79.

2. PEDIATRIC PULMONARY DISEASES

PROGRAM GOALS

Among childhood disorders involving the lung, cystic fibrosis, and hyaline membrane disease are health problems of national significance. Respiratory distress syndrome (hyaline membrane disease) is the most common cause of death in the newborn in the United States, and affects between 50,000 and 100,000 babies each year,

about half of whom die. Bronchiolitis, also covered in the National Program, is one of the major obstructive airway diseases of children and may be important in the development of adult chronic lung disease. The cause of respiratory distress syndrome of the newborn, the nature of cystic fibrosis, and the possible long-term effects of early childhood bronchiolitis need to be determined and understood.

- Until research has uncovered ways to prevent hyaline membrane disease, early diagnosis and prompt initiation of therapy are essential to save the lives of babies born with this disorder. Primary goals of this program are to develop improved methods for early diagnosis and to design more effective modes of therapy.

- Similarly, present modes of therapy for cystic fibrosis, a genetically determined disease, are at best palliative. The primary goal at this time is to develop a rational basis for therapy through an understanding of the pathogenesis of this disease.

- There is reason to believe that bronchiolitis in children may be related to chronic lung disease in the adult. Therefore, an important goal is to conduct long-term, follow-up epidemiologic studies of children who have had bronchiolitis.

RECENT PROGRESS

Two important breakthroughs have occurred in the detection and treatment of hyaline membrane disease. First, it is now possible to detect the disease before birth. Secondly, an important therapeutic breakthrough has occurred which dramatically reduces the mortality from this dreaded disease.

The novel and provocative diagnostic technique involves sampling amniotic fluid (amniocentesis) and promises to result in exciting new therapeutic and preventive measures. Surfactant material is produced and secreted by the fetal lung into the amniotic fluid. Thus, the surfactant levels in amniotic fluid reflect the fetal lung's ability to produce and secrete surfactant. A rapid and easy test of surfactant in amniotic fluid has been developed, and studies are underway to improve the accuracy of the diagnosis. The ability to predict hyaline membrane disease in the fetus permits the earliest possible medical care for the newborn child and opens up new avenues of approach to this disorder by detecting prematurity of the infant and preventing immaturity of the lung.

Survival of infants with hyaline membrane disease is usually determined within a matter of days to 1 to 2 weeks. Therapeutic efforts have focused on methods of keeping the airways patent and maintaining adequate oxygenation of the blood through artificial ventilation and other aspects of intensive care usually available in

large hospital centers. Unfortunately, this was not sufficient and more than half of these infants died. A provocatively simple technique, albeit one that requires scrupulously attentive patient care, has resulted in survival of up to 90 percent of these babies. This therapy, known as continuous positive airway pressure (CPAP), is used in conjunction with artificial ventilation. CPAP keeps the lungs expanded and the oxygen exchanging portions open and functioning. Thus, the blood is readily oxygenated and the baby's overtaxed heart is relieved. CPAP still requires further study since it may result in circulatory alterations and possibly adverse effects on the airways. However, many of these problems can be overcome through application of available intensive care techniques. With increasing acceptance of this exciting therapeutic achievement by neonatal intensive care units throughout the country, the mortality due to this disease should be drastically reduced.

A conference has been held which explored the clinical aspects of cystic fibrosis and its treatment as well as the underlying genetic and physiologic alterations. Although this disease affects many organs, the pulmonary impairment which may be related to recurrent infections and abnormalities in mucus production commonly causes disability or death. The Institute's program is addressed to evaluation of cardiac and pulmonary functions and their alteration with therapy. The biochemistry of the mucus abnormality is also being investigated, and a meeting has been held to exchange information and stimulate new approaches in the study of mucin.

Several groups are engaged in research on methods for early diagnosis of airway disease in newborns and young children. A spirometer designed for compliance measurements in premature and term newborn infants is in the developmental stage. A system which is designed to measure pressure-volume curves of the lung and thorax, and functional residual capacity in anesthetized subjects is also being evaluated. Investigators have initiated a long-term study of effects of viral lower respiratory tract illness in children on later development of adult lung disease. Serum alpha-1-antitrypsin (an enzyme) activity and serum antibody titers to common respiratory viruses are being measured in children with bronchiolitis.

FUTURE CHALLENGES

Understanding the biochemistry and molecular biology of surfactant during normal maturation and hyaline membrane disease in order to develop methods of modifying or preventing the disease is a major challenge. Therapy for hyaline membrane disease should be improved by development of new devices and approaches and ways to initiate treatment as soon as possible. The efficacy of present methods of treatment needs to be assessed and knowledge about such methods widely disseminated. A better understanding of the etiology and pathogenesis of hyaline membrane disease is expected with new methods of prevention and improved therapy.

The cause of the mucus abnormalities in cystic fibrosis and the pulmonary derangements which result must be discovered before effective and meaningful therapeutic and preventive measures can be undertaken.

As a first step in determining whether bronchiolitis in childhood predisposes to chronic lung disease in the adult, criteria for diagnosis of bronchiolitis and protocols for long-term study need to be established.

ACTIONS

The Institute plans to:

1. Extend interdisciplinary studies of biochemical changes associated with hyaline membrane disease through Specialized Centers of Research. In addition, programs will be initiated to study biochemical changes associated with the development of cystic fibrosis.

2. Test various supportive measures for patients with cystic fibrosis, including mist-tent therapy and bronchodilators.

3. Improve management and therapy of hyaline membrane disease through the development of programs for rapid transfer of infants with this disease to intensive care units. Programs will be initiated for research and development of new or improved devices for treatment and controlled clinical trials of available methods of treating hyaline membrane disease and cystic fibrosis.

4. Initiate epidemiologic studies to determine prospectively the long-term effects of bronchiolitis in childhood on the occurrence of chronic lung disease in the adult.

SCHEDULE

Because recent findings hold great promise for an effective therapeutic approach to hyaline membrane disease, and because of increasing awareness of the importance of the pulmonary manifestations of cystic fibrosis to morbidity and mortality from this childhood disease, the programs in pediatric pulmonary diseases will be increased beginning in FY 75 and maintained at a level that includes modest increments until FY 79, when a levelling off will occur. Since early initiation of treatment of hyaline membrane disease is essential for infant survival, the NHLI will initiate early in FY 75 plans for a program of recognition and early treatment of neonatal respiratory insufficiency and respiratory failure. During this period, there will be a phase-in and gradual expansion of the education program, described in the section on Prevention, Control, and Education.

3. EMPHYSEMA AND CHRONIC BRONCHITIS

PROGRAM GOALS

Chronic obstructive pulmonary disease (COPD) is a major health problem in this country. Each year, direct and indirect costs of COPD amount to approximately $1.8 billion and 90,000 man-years of lost productivity. Emphysema and chronic bronchitis are the two main diseases which, when considered together, are referred to as COPD. Both emphysema and chronic bronchitis produce breathlessness, cough, and increased susceptibility to respiratory failure and death. COPD attacks middle-aged men and women and is particularly common in smokers. It is now believed that early abnormalities (physiologic and biochemical) related to emphysema and chronic bronchitis may be detected at a stage when lung damage is still reversible.

- Because of the nature of these disease problems, a goal of the program is to prevent development of these diseases by early diagnosis and identification and control of risk factors.

- At the same time, because of the great number of individuals suffering from already established and progressive disease, another goal is to improve treatment and rehabilitation programs.

- To understand the mechanisms and causes of these diseases is also an important goal and will be greatly aided by the development of basic knowledge of normal lung biochemistry, metabolism, response to injury, and repair processes. (See the section on Structure and Function of the Lung.)

RECENT PROGRESS

Emphysema is the fastest growing cause of death in the United States and is now the third leading cause of death from respiratory disease. The NHLI is currently placing major emphasis on efforts to identify the risk factors of COPD. There are many different kinds of emphysema, none well understood. Cigarette smoking has long been recognized as a major risk factor for emphysema, but attempts to identify other causes and risk factors have often ended in failure. New lines of research have opened up through the recent discovery of a genetic basis for one type of emphysema. Environmental risk factors are being identified in a variety of occupations.

A genetic enzyme defect known as alpha-1-antitrypsin deficiency has recently been identified as a factor in the development of emphysema. When inherited from both parents, this enzyme defect has been shown to be associated with the development of a severe form of familial emphysema which attacks young adults. This

emphysema is rapidly progressive, resulting in death by the early 40's--a time of peak earning potential and productivity. It is not known for sure whether individuals with only one gene for the defect (i.e., inherited from only one parent) are also at higher risk, but early results indicate that at least one group of such carriers may be at particularly high risk.

Alpha-1-antitrypsin deficiency may be responsible for as much as one-third of the emphysema in the United States today. Early detection and treatment can do much to prevent this tragic waste.

A screening test for alpha-1-antitrypsin deficiency has been developed. This test is now being performed on a number of population groups to determine the frequencies of the affected and carrier states, and to identify persons who are affected but who have not yet developed emphysema, in order to begin preventive treatment and possibly genetic counseling. At the same time, investigations are underway to define the underlying genetic defect and to find possible methods for prevention of the associated emphysema.

Early detection is an important step toward prevention of COPD. A new and promising method has been developed for the early detection of changes in lung function and structure which appear to be the first sign of chronic obstructive pulmonary disease. This method, measurement of closing volume (the amount of air remaining in the lungs after smaller airways collapse at the end of expiration), detects early changes in the lung which are thought to eventually progress to the clinical signs and symptoms of COPD. It is presently believed that in persons with abnormal closing volume measurements, but with otherwise normal lung function tests, the progression of disease may be reversed and the development of disabling disease prevented with proper treatment and the cessation of smoking. This method is being used on selected populations to evaluate its usefulness in mass screening of COPD. A standardized protocol for using the method has been prepared to assure comparability of different studies.

A workshop on animal models for emphysema was held which identified new areas for research into the basic mechanisms of this disease. Because cigarette smoking plays a key role in the development of COPD, animal models for smoking are being developed to identify the agents and mechanisms responsible for lung damage caused by smoking. Many investigators are working to define the role of certain enzymes, particularly proteolytic enzymes, in the development of emphysema. The role of macrophages (a cell found in the lung) in the development of emphysema and chronic bronchitis is also being investigated.

Advances made in the understanding of the structure and function of the lung (described in the preceding section) will also be important to the eventual success in controlling chronic bronchitis and emphysema.

FUTURE CHALLENGES

Recent research progress has been achieved in identifying genetic factors associated with COPD. The most immediate challenge for the future is how to influence people who are at risk, because of genetic factors, to modify their life style in order to avoid environmental risks that may lead to COPD. Another challenge is to identify the factors in cigarette smoke that produce lung damage. Studies to determine the mechanisms by which the lung clears itself of particles inhaled in cigarette smoke, the modification of these mechanisms by pollutants in the environment, and prospective epidemiologic studies of individual differences in response to the harmful effects of tobacco are planned or in progress. Measures to modify the smoking habits of the population need to be developed in collaboration with behavioral scientists, and especially needed are programs to decrease smoking in the young.

Other host factors, some genetic in origin, may be determinants of emphysema and chronic bronchitis. A systematic search for inherited enzyme abnormalities that predispose to development of COPD is an essential part of the program on host factors.

We need to develop improved techniques and devices to detect biochemical, immunologic, or physiologic abnormalities associated with emphysema and chronic bronchitis sufficiently early to effect reversal of the process, something now believed possible. The closing volume test has been shown to be abnormal significantly more frequently in smokers than in nonsmokers--in fact, few smokers show normal test results. However, the full significance of this test is still unclear, and studies are in process to determine the relationship of an abnormal closing volume measurement to future development of COPD. If, indeed, it can be documented through preliminary screening studies that this test can identify persons with a potentially reversible (and preventable) stage of COPD, then we will have a potent new screening test that can be applied to large populations in order to detect early disease at a stage when cure can be accomplished.

ACTIONS

The Institute plans to:

1. Develop a multidisciplinary program addressed to the problem of smoking. This program will include investigation of the mechanisms and agents responsible for cigarette smoke injury in emphysema and chronic bronchitis, as well as efforts to modify smoking habits by means of psychological and pharmacological approaches.

2. Elucidate the role of host factors, including genetic ones, in the development of emphysema and chronic bronchitis by conducting and extending epidemiological studies.

3. Enlarge efforts in emphysema and chronic bronchitis prevention through the development of improved techniques and devices for early detection of reversible diseases and application of new knowledge from studies of risk factors and their control. Epidemiological screening studies may be required at a later date if this program proves successful.

4. Initiate controlled clinical trials to evaluate the efficacy of current and newly developed approaches to therapy and rehabilitation.

SCHEDULE

Present programs relating to pathophysiology and diagnosis of advanced disease are being reduced in FY 74 and will be further reduced by FY 80. Current and new actions in emphysema and chronic bronchitis research are being increased. By early FY 75, a collaborative study on the closing volume test will be extended to population screening for early airways disease, and a joint program will be initiated with other Federal and state agencies on the role of chronic bronchitis in the development of coal miner's pneumoconiosis. New activities in early diagnosis, clinical trials, and multidisciplinary approaches to smoking reflect increased efforts through FY 80. Development of increased interagency contact, begun in FY 74 between the NHLI and the National Institute of Mental Health to identify studies of mutual interest regarding behavior, smoking, and lung disease, will be pursued. Host factor research will decrease in FY 76 as ongoing programs on alpha-1-antitrypsin are concluded. As new information on other host factors becomes available, this program approach will increase in activity again in FY 78.

4. FIBROTIC AND IMMUNOLOGIC LUNG DISEASES

PROGRAM GOALS

Fibrotic and immunologic lung diseases result from the interaction of a variety of environmental and host factors. These include viral and bacterial infections, diseases of the connective tissue, radiation damage, exposure to substances such as molds and dust that initiate hypersensitivity reactions, and inhalation diseases resulting from exposure to substances such as coal dust, silica, asbestos, and pollutant gases such as nitrogen dioxide, ozone, and sulfur dioxide. Fibrotic and immunologic lung diseases can be prevented or treated if the offending substances can be removed or their effects suppressed. Therefore, a primary goal of the National Program in this area is to disseminate information about the causes of these diseases, as these are discovered through research, and how to avoid them. (See section on Prevention, Control, and Education). The Institute's current research program on fibrotic and immunologic lung diseases

focuses on asthma, pulmonary fibrosis, hypersensitivity pneumonitis, and noninfectious granulomatosis. In cases where exposure cannot be avoided or the disease prevented, effective treatment depends on understanding the processes leading to disease and minimizing their impact on the lungs.

- The research goal is to conduct fundamental investigations essential to the development of improved therapy.

RECENT PROGRESS

Asthma is an immunologic disease specifically mentioned in the National Heart, Blood Vessel, Lung, and Blood Act of 1972. The NHLI program focuses primarily on the nature of the pulmonary functional impairment. To learn more about the unusually irritable airways of asthmatics, the possible interaction between the inhaled antigens that stimulate bronchial spasms and nonantigenic inhaled pollutants (e.g., sulfur dioxide) are being studied, and the effects of pharmacologic mediators (e.g., histamine) are being evaluated. Immunologic and allergic bases of asthma are research areas within the mandate of other NIH Institutes.

Early diagnosis of fibrotic and immunologic lung diseases, while they are still reversible and curable, is a primary research objective. The methacholine challenge test for detecting preclinical asthma is currently undergoing evaluation. A multidisciplinary group is identifying specific antigens associated with hypersensitivity pneumonitis and preparing and testing diagnostic skin tests. Other investigators are utilizing animal models to investigate the role of the immune system in these disorders and to seek ways to develop early diagnostic tests.

Studies in asthmatics following exercise have been performed and will now permit attempts at modifying the course of the response. Approaches to therapy include: investigations of lung innervation to provide an understanding of neural control of bronchoconstriction and the basis for developing rational pharmacologic therapy; studies of lung mechanics, gas exchange, and blood flow to determine precise clinical indications for bronchopulmonary lavage--a therapeutic measure used in some resistant asthmatic attacks; and studies of behavioral conditioning as a possible way of controlling respiratory resistance in asthmatics.

Pulmonary fibrosis, which may result from chemical, physical (radiation), and microbial injury as well as hypersensitivity reactions, includes a group of diseases for which no apparent cause has been identified. Studies are underway to elucidate the immunologic mechanisms that lead to pulmonary injury. Basic information

is being developed regarding connective tissue protein metabolism (collagen and elastin), and a major effort is being made to stimulate research in this area. Methods for studying cell-mediated immunologic responses and circulating antibodies in humans and animals have been developed and applied to lung diseases.

Hypersensitivity pneumonitis, usually a consequence of inhalation of allergens, occurs among pigeon breeders, farmers, and workers exposed to detergent enzymes. Several multidisciplinary centers are conducting research focused on the epidemiology of hypersensitivity and diffuse interstitial lung diseases. Technology for mass screening, both in pulmonary function and immunology, has been developed to facilitate epidemiologic studies, and population groups have been identified and are being studied. Attempts at correlating the levels of exposure with functional and structural deterioration of the lung will hopefully result in improved and safer environmental and industrial standards.

Among noninfectious granulomatoses, sarcoidosis is of particular epidemiologic interest due to its unusual prevalence among the black population in this country (10 to 17 times more common than in the white population) and because it is twice as common among females as among males. An epidemiologic study of sarcoidosis is being developed.

Animal models of fibrotic and immunologic lung diseases have been developed and are valuable for investigating etiologic and pathogenetic mechanisms. An animal model of allergic asthma is now available and is being used to study the neurologic mechanisms in this disorder. Several multidisciplinary projects are utilizing animal models of hypersensitivity and diffuse interstitial lung disorders, and a program is being initiated to develop animal models of sarcoidosis.

FUTURE CHALLENGES

Where population groups are known to have a high prevalence of pulmonary fibrosis or immunologic lung diseases, epidemiological studies should be carried out to identify the factors responsible. This identification of specific etiological agents is crucial to the development of effective control measures aimed at eliminating these factors. The Institute will seek to coordinate epidemiologic programs through use of standardized methods and protocols and increased communication, so that data can be compared.

Advances in biochemistry, pharmacology, and immunology have not yet been brought adequately to bear on problems of lung disease. These basic scientific disciplines need to be drawn upon in the development of therapy, prevention, and control of immunologic and fibrotic lung diseases. Understanding the role of certain endogenous mediators and their composition and mechanism of action, though difficult to achieve, is essential. The specific roles of molecular mechanisms involved in cell-mediated and antibody-mediated

immunologic responses in lung disease must be defined. It is anticipated that the inflammatory and bronchoconstricting responses mediated by certain hormonal agents will be better understood in the future. The mechanisms of collagen synthesis and degradation need to be studied in order to develop therapy directed at specific events in the chain of metabolic changes leading to disease. It is anticipated that specific components of collagen will be identified and that improved methods of assaying elastin will allow better understanding of its metabolism in the lung. Techniques for diagnosing sarcoid are being developed, and a better understanding will be sought of immunologic and neurologic mechanisms of fibrotic and environmental lung diseases, asthma, and sarcoid.

Many animal models of immunologic and fibrotic lung diseases are available and represent opportunities for study of the pathogenesis of these diseases.

ACTIONS

The Institute plans to:

1. Seek new information about the synthesis and degradation of collagen and the immunologic responses and defense mechanisms of the lung through continued and extended multidisciplinary programs. These will involve collaboration by immunologists, biochemists, physicians, and physiologists.

2. Initiate programs to develop pharmacologic agents that will modify the alterations in connective tissue metabolism that lead to pulmonary fibrosis, and study the use of immunologic techniques to stimulate tissue defense mechanisms against immunologic lung diseases.

3. Initiate epidemiologic studies to investigate etiologic factors in population groups characterized by unusual prevalence of fibrotic and immunologic lung diseases.

SCHEDULE

Attention currently focuses on characterizing the lung structural proteins, collagen and elastin, at the biochemical level. Programs which are oriented to the synthetic and degradative processes of collagen and elastin are being implemented. Programs concerned with epidemiology, animal models, and development of a simple *in vitro* test of sarcoidosis will continue through FY 78. Epidemiologic studies of hypersensitivity pneumonitis and fibrotic lung disease will begin to produce useful information on the pathogenesis and natural history of these disorders by FY 77. By redirecting funds from other program areas, both new actions and the total program in fibrotic and immunologic lung diseases will undergo a substantial increase between FY 76 and FY 80. All of the action areas--multidisciplinary approaches, targeted programs, etiology and epidemiology--reflect incremental activity between FY 76 and FY 80.

5. RESPIRATORY FAILURE

PROGRAM GOALS

Respiratory failure may occur in many different disorders, both acute and chronic, pulmonary and nonpulmonary. Despite considerable progress in the development of sophisticated therapy, respiratory distress syndromes (acute respiratory insufficiency) of the adult remain among the most common causes of postoperative mortality and of death related to major trauma. Because acute respiratory insufficiency is potentially reversible if recognized early and if treatment is initiated promptly, the major research emphasis at present is on identification of factors that predispose to these syndromes, studies of the effects of oxygen toxicity, and development of therapeutic devices, especially ventilatory assist devices and oxygenators. (See section on Respiratory Assistance.)

- A program goal is to develop improved techniques for detection of potential respiratory failure.
- Another goal is to develop monitoring devices and modes of therapy that are less costly, less complicated to administer, and more readily available than those now in use for respiratory failure.

RECENT PROGRESS

Various techniques and devices have been developed for detecting impending respiratory failure. A sensitive spirometer that measures the peak acceleration which occurs early in forced expiration is currently being evaluated for its ability to detect early airway obstruction. Methods have been developed and are being evaluated for assessment of the degree of pulmonary edema. Powdered tantalum, as a roentgenographic contrast medium, has been clinically used to study the structure and function of bronchi, bronchioles, and alveoli in diseased lungs. Further developments relative to treatment of respiratory failure are discussed in the section on Respiratory Assistance.

FUTURE CHALLENGES

The specific challenges in this area are to improve the devices and techniques used to detect potential respiratory failure and to provide the attending physician with a better description of lung function during the period of respiratory failure, thus making it possible for the physician to be more responsive to the need for improved respiratory care during this critical care period. We need to evaluate critically current devices and techniques for early detection and subsequent monitoring of respiratory failure. New devices that can be easily used by physicians and allied health personnel need to be developed to provide more effective management. As new devices and techniques are developed, their efficacy must be tested in controlled clinical trials.

Future challenges include the development of a portable, rugged, and reliable mass spectrometer for continuous measurements of respiratory gases. Also, microsized, reliable, and stable electrodes need to be developed for the continuous *in vivo* gas measurements of pO_2 and pCO_2. In addition to the improved, continuous measurement of respiratory and blood gases, a more complete assessment of changes in pulmonary function and structure during the period of respiratory failure is a significant challenge. The development and evaluation of new noninvasive devices and techniques are required to support the therapeutic measures provided in critical care settings. A newly developed technique to continuously measure the ventilation/perfusion ratio may provide an important contribution. In addition, new and innovative techniques of lung imagery hold promise for monitoring lung function.

Despite the fact that respiratory support with positive pressure and high oxygen concentrations presently provides the basis for therapy during respiratory failure, the long-term effects of high oxygen concentrations and continuous mechanical ventilation on the lung are still not well understood. Further studies on the effects of long-term ventilation, with and without positive pressure, on the lung function and structure are needed. In addition, studies of the potential dangers to the lung of high oxygen concentrations for extended periods must be continued in order to complete our understanding of this problem.

ACTIONS

The Institute plans to:

1. Initiate development of devices and techniques for monitoring of respiratory function in patients with impaired lungs.

2. Develop and test improved invasive and noninvasive instruments for blood and respiratory gas analysis in patients with lung disease.

3. Develop devices and techniques to detect and monitor resistance in small airways and structural and functional abnormalities of diseased lung. (See section on Emphysema and Chronic Bronchitis.)

SCHEDULE

During the coming year, the initial phase of several programs in Respiratory Failure will be completed. The design and development of a lightweight, sensitive, and reliable mass spectrometer will be completed and ready for clinical test and evaluation. Likewise, the design, fabrication, and feasibility test for two new types of continuous, *in vivo* blood gas sensors will be completed, and the clinical use of the continuous ventilation/perfusion technique will be evaluated. Program development will subsequently continue to increase gradually through FY 79 with primary emphasis on providing improved diagnostic and monitoring capabilities.

6. PULMONARY VASCULAR DISEASES

PROGRAM GOALS

Pulmonary vascular diseases, which include cor pulmonale, pulmonary hypertension, and pulmonary edema, are serious lung disorders with often devastating consequences, and as such are the focus in this new program area in lung diseases. Reliable data on incidence and prevalence of pulmonary vascular diseases, as well as on the effectiveness of present modes of therapy, are not available. This is largely because present methods for diagnosis and for assessing therapeutic progress involve procedures that cannot readily be used on very ill or large numbers of patients. If these diseases could be reliably identified early in their course they could be effectively treated. If simple techniques that could be used repeatedly without undue discomfort to the patient were available, it would be possible to study the course of these disorders and assess the long-term benefits of therapy. The causes and development of these diseases need to be investigated through the use of animal models in an interdisciplinary setting.

- A primary goal of this new program area is to stimulate development of reliable, noninvasive techniques for assessing the ventricular hypertrophy associated with cor pulmonale, and for diagnosing pulmonary hypertension without the need for cardiac catheterization.
- Another goal is to encourage development of animal models of cor pulmonale and pulmonary hypertension to be used in the investigation of pathogenetic mechanisms of these diseases.
- Multidisciplinary studies must be fostered toward understanding the dynamics of fluid, electrolyte, and protein exchange in pulmonary edema.

RECENT PROGRESS

Although it is not accurately known how many patients suffer from cor pulmonale, this disorder is most often a consequence of emphysema and chronic bronchitis, themselves chronic respiratory diseases of national impact. Autopsy data suggest that pulmonary hypertension is also underestimated because at present it can only be diagnosed by catheterization, a procedure not amenable to screening large numbers of persons or to use in the very ill. Pulmonary edema is more prevalent than generally realized but is usually reported only when it is the admitting diagnosis and not when it arises in the course of hospitalization or is treated in the outpatient clinic. It is a common occurrence in cardiovascular and renal diseases, as well as in many pulmonary disorders. With the methods presently available, pulmonary edema can only be detected late in its clinical course, making prompt therapy of the condition impossible, and thus contributing to its morbidity and mortality.

FUTURE CHALLENGES

Early diagnosis is the first step in treating these pulmonary vascular diseases effectively while they are still reversible. To evaluate the efficacy of therapy, serial assessments must be made of the patient's condition over long periods. Both of these needs depend upon development of reliable techniques that are noninvasive, safe, and cause minimal discomfort to the patient. Some noninvasive techniques have been developed, but none have sufficient promise to meet the clinical needs for diagnosing and screening for pulmonary hypertension, cor pulmonale, or pulmonary edema. A major challenge is to develop promising diagnostic techniques which would make it possible to screen large numbers of persons. These techniques would be used to identify population groups for the study of etiologic factors and pathogenetic mechanisms, and for assessing therapeutic regimens.

New and better animal models need to be developed in the future to study the pathogenesis and pathophysiology of cor pulmonale and pulmonary hypertension at the molecular and biochemical levels, and to further assess diagnostic and therapeutic techniques. Available animal models do not adequately represent the disease processes known to occur in humans. Fundamental studies are also needed to elucidate neural, endocrine, and electrolyte factors in the pathophysiology of pulmonary hypertension. Limited work in this area shows great promise of yielding information necessary for future preventive, therapeutic, and diagnostic efforts. Studies of the lung's interaction with vasoactive materials and of the ultrastructural and biochemical aspects of vascular smooth muscle need to be extended.

The early diagnosis and prompt therapy of pulmonary edema require a thorough understanding of basic pathogenetic mechanisms in terms of ultrastructural, metabolic, and molecular changes. Results to date suggest that these approaches will pay large dividends, and extension of this work with application of new approaches is necessary.

ACTIONS

The Institute plans to:

1. Extend multidisciplinary efforts to elucidate the dynamics of exchange of water, protein, and electrolytes, the biochemistry of edema fluid, and metabolic alterations in the edematous lung.

2. Encourage the development of safe, noninvasive methods for detecting pulmonary hypertension, cor pulmonale, and pulmonary edema. These methods or devices should be sufficiently sensitive to assess both the presence and progression of the disease.

3. Promote multidisciplinary approaches on the pathogenesis and pathophysiology of cor pulmonale and pulmonary hypertension. Investigators will be encouraged to develop animal models of these diseases, to apply ultrastructural and biochemical techniques to the study of vascular smooth muscle, and to study the metabolism of vasoactive amines by the lung.

4. Develop epidemiologic programs aimed at determining the true impact of cor pulmonale and pulmonary hypertension on the population, identifying host factors and other agents responsible for the etiology and pathogenesis of these diseases, and collecting patient populations for evaluating diagnostic and therapeutic methods.

SCHEDULE

The above actions will be initiated in FY 75, and these efforts will be increased gradually through FY 78.

7. INHALATION DISEASES

PROGRAM GOALS

This new program area is addressed to respiratory diseases that result from the direct effects of inhaled dusts, vapors, or gases and which can be prevented by removal of the offending substances or by protecting individuals from them. Therefore, a primary goal of the National Program is to disseminate information about the causes of these diseases and how to avoid them. (See section on Prevention, Control, and Education.)

- The research goal is to improve detection of the known causes of these diseases and thereby prevent their development.

RECENT PROGRESS

A great deal is already known about types of environmental agents that are associated with industries and occupations. Industrial progress often brings related problems; it has brought us many benefits, but also pollution. The introduction of the pneumatic drill was a tremendous boon to the mining and construction industry, but it also greatly increased the incidence of lung disease caused by the inhalation of dust particles in the air. Of all occupational illnesses, dust inhalation diseases, medically known as pneumoconioses, are the most serious health problem. The dusts responsible for pneumoconioses are not the familiar dusts we wipe off our cars and furniture, but the heavy, often harmful dusts that millions of American workers (coal miners, insulation workers, foundrymen, stone cutters, and other occupational workers) breathe in every day on the job. So fine are these dusts that they escape the natural cleansing mechanism of the upper respiratory tract and lodge permanently, inextricably, in the lungs. Some are relatively harmless;

others can be deadly. Eventually, if exposure is sufficiently high and prolonged, the accumulated particles may cause fibrosis, or scarring of the lung tissue. In many cases, this leads to serious disability and even death.

FUTURE CHALLENGES

Not long ago, the hazard of pneumoconioses was considered confined to certain jobs in specific occupations. Today, it is recognized that the problem is far more complicated and that sources of these diseases have greatly widened. It has been found that not only are workers themselves potentially at risk, but also their co-workers and, in some cases, the community at large. This last possibility--environmental lung disease associated with agents usually encountered only by certain workers--has given the problem considerably more dimension and importance.

Authorities who have studied the problem believe that with the cooperation of Federal and state agencies, management and labor, practically all cases of pneumoconioses can be prevented. Each dust-producing job must be studied to decide the best method of prevention. Sometimes dust levels can be reduced easily by proper ventilation of work areas, removal of dust by suction as it is produced, wetting down of materials before they are worked on, or by switching from a hazardous material to one that does not cause disease. In other cases, the control of dust diseases is an extremely complicated matter, involving elaborate and costly measures.

The pulmonary changes resulting from specific inhalation diseases are usually fibrotic in nature but may also involve immunologic alterations. Consequently, as more is learned about the causes of these disorders, it is anticipated that they may be transferred to the Fibrotic and Immunologic Lung Diseases program area.

ACTIONS

The Institute plans to:

1. Develop programs to improve the prevention, detection, and relief of inhalation diseases.

SCHEDULE

The Institute's program on inhalation diseases will emphasize Prevention, Control, and Education efforts. Research on detection and relief of inhalation diseases will be initiated in FY 75 and gradually increased through FY 78.

8. RESPIRATORY ASSISTANCE

PROGRAM GOALS

The development of techniques and devices for providing respiratory assistance is an important component of the Institute's research efforts to combat all diseases of the lung, and especially respiratory failure, and as such is called out as a separate program area in this updated plan. Because respiratory failure is a debilitating and often fatal disorder that is an eventual complication of nearly every respiratory disease, the development of effective therapeutic devices is of the greatest importance.

- The major goal of this program area is to apply new technology to the treatment of respiratory failure and to develop improved rehabilitation devices and techniques.

RECENT PROGRESS

The most significant progress in this program area to date has been the development and testing of membrane oxygenators in animals and humans. These oxygenators have demonstrated sufficient promise to warrant testing in clinical trials under highly controlled conditions. If such trials demonstrate the efficacy of the devices, they could become a valuable mode of therapy to be widely used in support of infants with respiratory distress syndrome and adults in respiratory intensive care units.

Research on respirators has led to development of a compact, portable, ventilatory-assist device which can be patient-cycled for the changeover from the expiratory to inspiratory phase. This device also has automated sigh capability and ability to provide a positive end-expiratory pressure. Clinical trials are presently underway.

Despite the therapeutic importance of oxygen inhalation devices for patients in respiratory failure, elevated concentrations of inspired oxygen may be potentially dangerous. A recent workshop provided a forum for review of research progress, exchange of views, and assessment of future needs to insure oxygen therapy without concomitant oxygen toxicity.

FUTURE CHALLENGES

An immediate challenge for providing prompt respiratory assistance is the clinical determination of which patients in respiratory distress may benefit from long-term (days) membrane oxygenator support and when in the course of their distress such support should be administered. Such criteria could provide needed direction to the effective clinical use of this new support device and the maximum exploitation of its potential.

Continued development of artificial lung systems is anticipated. New approaches and materials could lead to systems with greater clinical utility. For example, the search for and testing of new oxygenator materials may lead to a device that requires less complex blood management during its clinical use. Techniques of blood management required by currently available membrane oxygenators preclude their use in many patients requiring respiratory assistance.

The search for and testing of various materials for use in oxygenators will continue. These efforts will lead to improved management of patients with acute and chronic respiratory insufficiency. Progress is also anticipated in the development of noninvasive methods to assess lung function during respiratory insufficiency and to determine the subsequent need for oxygenator support.

ACTIONS

The Institute plans to:

1. Expand programs addressed to ventilatory-assist devices and oxygenators to insure improvements in available devices and development of new ones.

2. Test presently available and promising new devices in controlled clinical studies.

3. Develop programs to insure the early initiation of treatment.

4. Continue and extend Specialized Centers of Research where sophisticated techniques are available in order to capitalize on what is known and to improve present modes of therapy.

SCHEDULE

A collaborative program will be initiated soon to establish clinical criteria for the therapeutic use of membrane oxygenators in the management of acute respiratory failure. In addition, the design, fabrication, and feasibility studies for several new and novel oxygenator designs will be completed. Analysis and monitoring of other forms of respiratory assistance devices will continue to be increased in subsequent years, reaching a peak by FY 78, in order to provide more effective support to those in respiratory distress.

BLOOD DISEASES AND BLOOD RESOURCES

The NHLI program in Blood Diseases and Blood Resources is intimately related to the Institute's responsibilities in cardiovascular and pulmonary diseases. Blood is a vital part of the circulatory system since it is the vehicle in which oxygen, nutrients, and other body chemicals are carried through the blood vessels to every part of the body, to be exchanged for carbon dioxide, waste products, and chemicals which in turn need to be transported away.

Problems in the blood are often reflected in disorders of the cardiovascular and pulmonary systems. Life-threatening situations can arise if the blood clots within the heart, blood vessels, and lungs, or if it escapes from the cardiovascular system, as in hemorrhage, into the tissues (e.g., stroke) or outside of the body. Blood that has lost its capacity to clot, such as in the bleeding disorders (e.g., hemophilia) can also give rise to life-threatening situations.

Blood is an organ in its own right, composed of many different elements. In addition to the important functions mentioned above, it participates in the body economy in a number of ways. It contains important chemicals such as hormones and enzymes, protective agents (antibodies) against certain diseases, factors important in preventing clotting of blood within the cardiovascular system, and factors important in promoting clotting of blood when it accidentally escapes from within the heart and blood vessels. The blood cells defend the body against invading organisms and aid in the repair of organs, including the vascular system and the lungs. An adequate volume of blood within the circulatory system is important in maintaining normal blood pressure and perfusion of blood to all parts of the body.

Blood is a very important life-saving therapeutic tool in medicine as well as in surgery. Millions of Americans are saved each year by blood or blood component therapy. Many of these individuals would previously have met with certain death. Almost 10 million units of blood and 1.7 million liters of plasma (the equivalent of an additional 8.5 million units of blood) were collected in the United States in 1971 for use in therapy. Studies of blood preservation and efforts to reduce immune responses to transfused blood are important in the area of organ transplantation as well.

The plans for developing the Institute's program on blood diseases and blood resources as well as the plans for coordination of the National Program were outlined in the National Heart and Lung Institute Summary (Volume 1) of the National Heart, Blood Vessel, Lung, and Blood Program on May 1, 1973.

The updated National Program presented here represents an orderly review and assessment of NHLI activities in the field of blood diseases and blood resources and continues to be responsive to the Legislative Act which specifically requires "studies and research into blood diseases and blood, and into the use of blood for clinical purposes and all aspects of the management of its resources in this country . . . ."

The program goals, actions, and schedules as set forth in 1973 in the National Program, have been reviewed and updated by the Institute and its advisors. Recent progress and future challenges for each program area have been identified. This updated Program for the next five years, together with the recent progress and future challenges identified, are presented here.

The four areas addressed by the Institute's research programs in blood are:

1. Bleeding and Clotting Disorders
2. Sickle Cell Disease and Related Disorders of the Red Blood Cell
3. Biomaterials
4. Blood Resources.

The first, second, and fourth program areas were identified separately in 1973; the third, already included in the 1973 Plan, is given separate status in the updated research program presented here. In revising its Plan for blood diseases and blood resources, the Institute has modified some Actions and integrated others, resulting in an overall decrease of 15 specific research Actions in the updated Plan. These modifications in the program are made in order to take advantage of recent progress and future challenges.

1. BLEEDING AND CLOTTING DISORDERS

Blood clotting abnormalities are a major cause of death and disability in the United States. The National Program addresses two important areas related to disordered hemostasis: the hemophilias and the thromboembolic disorders. In the case of the hemophilias, life-threatening situations occur as a result of excessive uncontrolled bleeding because of failure of the patient's blood to clot normally. In the case of thromboembolic disorders, the opposite is true: the blood clots too readily, e.g., in the heart, the brain, or the lungs, causing life-threatening complications such as heart attacks, strokes, or pulmonary embolism.

The Hemophilias

PROGRAM GOALS

The hemophilias constitute a major national health problem for several reasons. First, treatment must be continued throughout the patient's lifetime at enormous costs; the alternative is crippling and death. Second, treatment of this single disease places one of the largest demands on the nation's blood supply. Finally, the impact of this disease on the patient and his immediate family is catastrophic in terms of social, psychological, and economic costs. The hemophilias are a family of hereditary disorders in which the patient's blood clots very slowly or not at all causing uncontrolled bleeding on injury or during surgery unless the appropriate clotting factor is supplied promptly.

- A major goal of this program is to understand the genetic mechanisms which result in the bleeding disorders known as hemophilias.
- A second goal is to improve methods of preparing and distributing the necessary plasma fractions so that they are available to all who need them at reasonable cost.
- A third goal is to allow the hemophiliac and his family to improve the quality of their life and to make informed decisions about their future, through programs of education, screening, and genetic counseling as described in the section on Prevention, Control, and Education.

RECENT PROGRESS

Research advances in the last two decades have completely changed the outlook for hemophilia care. The clotting factors needed by the hemophiliac have been identified, partially characterized and can now be mass produced from normal donor plasma. Given the increasingly more sophisticated management of our national blood resource, the hemophiliac can look to better, cheaper, and more widely available products for the treatment of his disease. Recent experiments in self-administered home care provide the basis for the expectation that antihemophilic factor may be used, as is insulin in diabetes, to prevent the manifestations of hemophilia--the crippling, suffering, expense, and time loss from school or work that have been characteristic in the past. Recent experiments also indicate that it may be possible to identify the carrier state in the prospective mother and through genetic counseling to reduce the prevalence of the disease. The NHLI's national survey of hemophilia treatment provides an informational basis on which to develop effective plans for study and treatment of the disease.

FUTURE CHALLENGES

Additional progress can be expected in the medical management of hemophilia. It is likely that home therapy may become feasible and economical in the near future. Self-administration of antihemophilic factor (AHF) immediately upon the first sign of bleeding may help prevent serious side effects such as crippling of joints. There is the further possibility that AHF may eventually be used prophylactically by the patient in his home to prevent bleeding altogether. The concept of comprehensive long-term management of hemophilia has not yet achieved wide acceptance and methods of such management and counseling need further study and dissemination to the public and to the medical profession. (See section on Prevention, Control, and Education.) In the future it may also become possible to transplant normal blood-forming tissue into these patients, thereby permanently correcting the disorder.

Despite the research advances described earlier, basic knowledge of hemophilia remains incomplete. A fuller knowledge of the molecular structure of the clotting factors could lead to even better therapeutic approaches through the identification of biologically active molecular fragments. Furthermore, the application of newer technology can lead to greater production efficiency and reduction in cost of antihemophilic factor. Antihemophilic factor derived from animal blood should be studied clinically to determine its value in treating the occasional patient who develops an antibody to the human factor. One common complication of replacement therapy is the transmission of the hepatitis virus. Still to be fully explored are methods of removal or inactivation of the virus in antihemophilic factor preparations.

ACTIONS

The Institute plans to:

1. Support fundamental research on hemophilia, especially on the molecular structure of the clotting factors, the chemistry of protein fractionation, the physiology of the coagulation system, and molecular genetics; apply these investigations as they mature to solve the clinical problems, e.g., greater efficiency in the production of antihemophilic factor from donor blood, the identification of effector sites on the molecule, and the isolation of active molecular fragments; extend the clinical experiments which indicate that inhibition of the clot-dissolving system is useful in the treatment of the bleeding crises of hemophilia.

2. Establish Specialized Centers of Research for the bleeding disorders. These should cover the full range of disciplines necessary for a comprehensive approach to hemophilia care. They should provide for both basic and clinical research.

SCHEDULE

Current targeted research efforts are scheduled for completion by FY 75, while grant activities will expand through FY 77. New Specialized Centers of Research are planned for FY 75 through FY 77, and their support will peak in FY 77.

Thromboembolic Disorders

PROGRAM GOALS

Thrombosis (clotting of the blood within the blood vessels) and embolism (clot fragments carried in the blood from their site of origin) are often responsible for the crippling or lethal manifestations of heart and blood vessel diseases. They are implicated in several of the major causes of death in the United States. Arterial thrombosis plays a role in heart attacks, stroke, and chronic renal disease. Venous thrombosis can result in pulmonary embolism, a disorder which hospitalizes some 300,000 persons and contributes to the death of more than 50,000 patients annually. Thrombosis and hemorrhage in the microcirculation play primary or contributory roles in hypertension, stroke, diabetes, cancer, sickle cell anemia, and many other disorders affecting virtually every organ in the body. The relationship of thrombosis to atherosclerosis is of fundamental importance to the nation's health and has far-reaching therapeutic implications.

- The major goal is to increase understanding of the fundamental mechanisms of thrombosis, especially the role played by the individual components of clotting and their relationship to the microcirculation.

- A second goal is to facilitate detection and treatment of thromboembolic disorders.

The approaches to both venous and arterial thromboembolism share two important concepts: (1) their causes involve an interplay of the blood coagulation system, the platelets (one of the formed elements in the blood), the vessel lining, and the properties of flowing blood, and (2) application of previously accumulated and newly generated knowledge in these areas can be expected to provide health benefits to a large number of American people.

RECENT PROGRESS

Risk factors for thrombosis and embolism have been recognized and high risk clinical situations have been identified. It is clear for instance that patients suffering from hip fracture or undergoing hip surgery are at very high risk for venous thrombosis and subsequent pulmonary embolism. Patients, especially the elderly, who are immobilized for any cause are at high risk. Venous thrombosis commonly occurs as a complication of heart failure. Thrombosis is often the first overt manifestation of some forms of cancer. Women using oral contraceptives have an increased risk, and thrombus formation is the leading complication of prosthetic valves and vessels and of the rejection phenomenon in organ transplantation.

Recently, advances have been made in the sensitivity of diagnostic methods for detecting deep venous thrombosis. Pathologic evidence indicates that venous thrombosis is so common that it was found in more than 50 percent of autopsied patients who died from any cause. The vast majority of these had been unsuspected. There is both a pressing need and an opportunity for increasing the acuity of diagnostic methods.

Work in the last decade on the clot-dissolving agents, urokinase and streptokinase, demonstrates that these agents have an important potential as treatments for a wide range of thromboembolic disease. For example, it has been demonstrated that these agents significantly accelerate the resolution of clots in the lungs (pulmonary embolism).

Perhaps most exciting is the promise offered by drugs which prevent the formation of blood clots by inhibiting the aggregation of blood platelets in the blood vessels. Recent laboratory and clinical studies indicate that these agents may have an important potential in the prevention of a wide range of thrombotic disorders including heart attacks.

FUTURE CHALLENGES

Further efforts are needed to capitalize on past progress in methods for detecting venous thrombosis. Hepatitis-free fibrinogen must be made available for clinical clot detection studies. Further efforts are well justified to identify fibrin and fibrinogen breakdown products as a key to the diagnosis of thrombosis in the microcirculation.

In the treatment of thrombotic disease, the greatest opportunity exists for full exploration of the potential of the clot-dissolving agents, urokinase and streptokinase, for treatment of patients with heart attacks, certain types of strokes, and other thromboembolic complications of cardiovascular disorders.

Prevention of thrombotic disease would have by far the greatest public health effect and, fortunately, an opportunity is presented by recent studies of blood platelets and the demonstration that the platelet aggregation phenomenon is susceptible to drug inhibition. Clinical studies are urgently needed to identify the best drugs, the most appropriate drug regimens, and the clinical conditions in which they should be used.

ACTIONS

The Institute plans to:

1. Encourage fundamental research in thrombosis and in the relationship between thrombosis and atherosclerosis; support study of the function and pathophysiology of the microcirculation; study the relation between lipid metabolism and platelet function; and encourage study of the role of the coagulation system in sickle cell crises.

2. Support the development of techniques and instrumentation for sensitive, reliable, specific detection of thromboembolic disease.

3. Devise and support clinical trials of platelet-inhibiting drugs in the prevention of thrombosis in patients at high risk.

4. Conduct clinical trials of the efficacy of clot-dissolving drugs in the treatment of thromboembolic disorders, especially heart attacks.

SCHEOULE

Present targeted programs will be completed in FY 77. Basic research in clotting will receive increased support between FY 76 and FY 79. Trials of antithrombotic drugs and studies of methods for early diagnosis of thrombosis will receive additional support, with the former peaking in FY 77.

2. SICKLE CELL DISEASE AND RELATED DISORDERS OF THE RED BLOOD CELL

The three groups of disorders considered in this section include Sickle Cell Anemia and Sickle Cell Trait, conditions closely related to sickle cell disease such as Cooley's Anemia, and defects affecting the Red Blood Cell Membrane and Enzyme Systems.

Sickle Cell Anemia and Sickle Cell Trait

PROGRAM GOALS

Sickle cell trait, the most common inherited disorder in the United States, is believed to be present in more than 2 million U.S. citizens, primarily black. The trait is a relatively benign "carrier" form in almost all of these 2 million persons. However, approximately 1 in every 500 black babies is born with the life-threatening form of the disease called sickle cell anemia. Such individuals undergo painful episodes called sickle cell crises. The research goals of the sickle cell disease program are to:

- Develop improved therapy for sickle cell disease crisis; increase knowledge of the fundamental biology of the disease and its complications; and develop effective and acceptable methods for education, screening, and counseling.

The goal of educating the public and the medical profession about sickle cell disease is discussed in the section on Prevention, Control, and Education.

RECENT PROGRESS

Recent advances have been made in fundamental research on sickle cell disease. The disease is due to a genetically determined change in the chemical substance (hemoglobin) responsible for the oxygen-carrying capacity of the blood. The presence of the changed hemoglobin (hemoglobin S) is accompanied by distortions in the shape of the normally biconcave red blood cells carrying the hemoglobin, making these cells less able to survive in the blood circulation and less able to move freely through the smaller blood vessels. The presence of hemoglobin S in the red blood cells may lead to anemia (reduction in the number of red blood cells) and intermittent blockage of blood vessels, precipitating occlusive sickle cell crises.

The NHLI continues to coordinate the HEW Sickle Cell Disease Program initiated by the President in 1971. The major objectives of this program are: (1) to foster research and development both at the fundamental and clinical levels; (2) to initiate and expand community education, screening, and counseling programs; (3) to educate medical and allied health professionals about the problems of sickle cell disease; and (4) to improve clinical care for victims of sickle cell disease. The last three of these objectives are discussed further in the section on Prevention, Control, and Education.

Studies are currently in progress to develop information about the mechamisms involved in precipitating and sustaining the painful occlusive crises and to find ways to deal with it effectively. Recent results show that the sickling process may possibly be related to ATP (an energy-rich substance) depletion and calcium accumulation

in the cell membrane. The possibility of an associated zinc deficiency has been observed in some patients. The reasons for the increased susceptibility to infection in patients with sickle cell disease are being studied.

Techniques have been developed which improve the ability to detect, measure, and study the structure of abnormal hemoglobins, and to identify them in the prenatal period, in cord blood and at birth. Progress has also been made in screening and diagnostic testing of hemoglobin abnormalities.

It has now been demonstrated that intravenous urea is ineffective as an anti-sickling agent in patients in painful crises. However, the search for therapeutic approaches continues, and clinical studies are planned to test the efficacy of sodium cyanate, a promising new agent.

Collaboration has been developed with other institutions interested in sickle cell disease. An agreement has been entered into with the Center for Disease Control to continue to conduct workshops in hemoglobin detection techniques for the demonstration service projects, to set up a hemoglobin proficiency testing program for the Federally supported sickle cell projects, and to serve as a reference laboratory for abnormal hemoglobins during the coming year.

FUTURE CHALLENGES

Despite knowledge of the precise defect in the sickle hemoglobin molecule, the areas of ignorance about sickle cell disease are probably greater than the areas of understanding. Therefore, a balanced program must address a variety of problems, from understanding of the red cell to treatment of the patient and education of the community.

The biology of the red cell, the mechanisms of sickling, the effects of combinations of sickle hemoglobin and other abnormal hemoglobins, the effect on the red cell of agents that may prevent or reverse sickling are some of the problems that must be addressed to gain the knowledge necessary for rational therapy.

We must continue to search for therapeutic measures that are effective, safe, and simple. As promising therapies are developed, they must be tested in clinical trials. Better screening techniques need to be developed to detect hemoglobin variants, including sickle hemoglobin. We need simple, rapid, accurate, and reliable methods suitable for screening.

Projects in screening and diagnostic testing of hemoglobin abnormalities are presently in an early phase. Future challenges in this area include development of accurate prenatal diagnosis of abnormal hemoglobins and of innovative methods of education and genetic

counseling. The greatest immediate need is for dissemination of accurate information and for education of the public regarding the meaning of sickle cell trait and sickle cell anemia. (See section on Prevention, Control, and Education.)

In developing interfaces with other agencies and organizations, the greatest challenge for the future is to develop a well-coordinated and uniform approach in all Federal departments and agencies on matters pertaining to abnormal hemoglobins.

ACTIONS

The Institute plans to:

1. Sustain and expand support of studies to understand better the molecular structure of sickle hemoglobin, interactions of other abnormal hemoglobins with sickle hemoglobin, differences in flow patterns between normal and sickle red cells, and the effect of various agents on all of these.

2. Implement development and testing of improved techniques for screening and diagnostic testing of hemoglobin abnormalities in patients with sickle cell, Cooley's anemia, and other related blood diseases.

3. Continue to develop interfaces with other Institutes of the National Institutes of Health and other Federal agencies: National Institute of Arthritis, Metabolism and Digestive Diseases; Health Services Administration; Department of Defense; Department of Labor; and Veterans Administration.

SCHEDULE

In FY 75, more emphasis will be placed on control, including information, education, and demonstration as discussed later in the section on Prevention, Control, and Education.

Interfaces with other Institutes within the NIH (National Institute of Arthritis, Metabolism, and Digestive Diseases; General Medical Sciences) and other Federal agencies (Health Services Administration, Department of Defense, Department of Labor, Center for Disease Control, and Veterans Administration) will continue in the general area of hemoglobinopathies with emphasis on sickle cell disease and Cooley's anemia.

Cooley's Anemia and Related Hemoglobin Variants

PROGRAM GOALS

Anemia is a broad term which designates a decrease in the number of red blood cells. Cooley's anemia (thalassemia) is an inherited disease resulting from defective production of the hemoglobin molecule which in turn leads to rapid destruction of the patient's red cells.

On a worldwide basis, thalassemia is the most common inherited disease resulting from a single gene mutation. Reliable data on its prevalence in the United States are not available. However, it is estimated that it occurs in at least 5,000 Americans, largely of Mediterranean ancestry. The goals of the research programs in Cooley's anemia are to:

- Develop a simple screening technique to identify carriers; develop better information on the effectiveness of transfusion programs and means of removing excess tissue iron; determine the effectiveness of splenectomy (removal of the spleen) in thalassemia and explore other possible modalities of treatment; and increase fundamental knowledge regarding control of synthesis of the hemoglobin molecule with a view toward achievement of preventive measures.

RECENT PROGRESS

Several important advances have been made in this program area. A method has been developed to synthesize hemoglobin in a cell-free system using components isolated from human red blood cells. This has subsequently led to the determination that the molecular defect in Cooley's anemia is transmitted by a messenger RNA (a substance carrying genetic information). A biologically active messenger RNA has been isolated from bone marrow and peripheral cells in patients with beta thalassemia. Full understanding and subsequent control of this material may ultimately lead to the capability of controlling the error resulting in thalassemia.

Through a coordinated effort with other institutes and agencies, plans are underway to develop an inexpensive, accurate diagnostic test and to evaluate treatment of this disorder. Pilot studies have been conducted of a simple screening technique for Cooley's trait.

FUTURE CHALLENGES

We know a considerable amount about the molecular abnormality in Cooley's anemia, but we do not know how to correct it. Present treatment is limited to frequent transfusions. While this gives temporary relief from the anemia, it burdens the body with excess iron that cannot be eliminated. Development of a substance, free of serious side effects and effective in reducing the iron overload, would prolong the life of patients with Cooley's anemia. A rational basis for therapy will depend upon further understanding of events at the molecular level; therefore, fundamental research must be continued.

We presently have no simple, accurate method for screening for Cooley's anemia trait, and therefore, no way of identifying carriers. Such a technique needs to be developed. Future challenges include the standardization of methods and establishment of a bank of hemoglobinopathies which will provide laboratories with standards and controls, the development of better modes of diagnosis, better chelating agents (for removing excess iron), other treatment approaches and ultimately a method to alter the gene leading to the defect.

ACTIONS

The Institute plans to:

1. Continue efforts in Cooley's anemia in coordination with other Institutes at the National Institutes of Health and with other Federal agencies. These programs will include studies on the mechanism of hemoglobin synthesis, clinical research to determine the effect of splenectomy and transfusion programs on the course of the disease, development of agents for removal of excess iron, prenatal diagnostic approaches, and better laboratory methods for detecting the carrier state.

SCHEDULE

Most of the Institute's intramural program in blood diseases is directly concerned with the acquisition of fundamental knowledge in Cooley's anemia and sickle cell anemia. The two diseases are inseparably linked at the fundamental level and programs will be continued jointly. The programs for research in Cooley's anemia and related red blood cell disorders will increase gradually through FY 79 and will involve investigator-initiated as well as targeted efforts.

Red Blood Cell Membrane and Enzyme Systems

PROGRAM GOALS

Disorders of the red cell membrane and enzyme systems are responsible for a small but significant number of clinically important cases of anemia. Perhaps more importantly, the red cell provides an easily accessible model for studying physiologic mechanisms and metabolic controls common to many cell systems. Red cells preserved outside the body (as in blood prepared for transfusion) depend on intact metabolism and membrane function for survival and function. Therefore, better understanding of these systems is applicable not only to blood preservation, but also to the preservation of other body cells, tissues, and organs.

- The major goal of this program is to obtain fundamental answers about membrane structure, function, and intracellular metabolic activity and to apply this information to clinical medicine.

RECENT PROGRESS

Progress is being made in a number of areas important to understanding the membrane and enzyme systems of red blood cells. The properties of red blood cells which contribute to their viability and which support their physiologic function in the circulation are being explored, e.g., oxygen transport and regulation of metabolism. Also in progress are studies of physical properties such as deformability, adhesiveness, and viscosity; physicochemical factors involved in the interaction of blood cells with one another and with their suspending medium; and investigation of biochemical, clinical, hematological, and genetic factors in diseases in which there is an inborn error in the metabolism of the red cells. Other studies are concerned with the problems of transport across cell membranes, the relationship of chemical properties and functions to cell types, transition from fetal to adult characteristics of membrane transport, and effects of various agents and conditions on permeability.

FUTURE CHALLENGES

The mechanism of anemia resulting from the interaction of drugs and agents with G6PD (an enzyme) deficient red cells requires further study. Better understanding of the factors which regulate red cell metabolism is necessary in order to extend the preservation of red cells beyond a few weeks. Reference laboratories for diagnosing and investigating red cell membrane and enzyme disorders must be identified and supported. Efforts are being made to encourage those institutions that possess the capability of diagnosing rare red blood cell deficiencies to submit grant applications for the establishment of such facilities.

The primary challenge for the future is to identify areas that may be neglected, to stimulate interest in pursuing these areas, and to encourage investigators to collaborate with each other when this seems the most advantageous way of meeting national goals.

ACTIONS

The Institute plans to:

1. Continue to support research on normal and abnormal red cell enzyme and membrane disorders, and identify reference laboratories for the diagnosis and investigation of these abnormalities.

SCHEDULE

These activities will be expanded gradually in conjunction with investigator-initiated work in Cooley's anemia and related hemoglobin variants.

3. BIOMATERIALS

PROGRAM GOALS

An understanding of the basic interactions between blood and the properties of natural and synthetic materials is essential to the development of implantable diagnostic devices, circulatory assist devices, oxygenators, and other artificial organs, as well as the understanding of the genesis of arteriosclerosis.

- The goal of the program is to explore the interactions between blood and natural and synthetic materials in order to develop blood compatible materials for specific uses.

RECENT PROGRESS

Several classes of biomaterials show both promising biocompatibility and suitable mechanical properties for use in circulatory assist devices and oxygenators as discussed in the sections on Circulatory Assistance and Respiratory Assistance. Refined surface grafting and bonding processes have made possible the development of improved cannulas for a variety of applications. Tissue culture research has opened the possibility of lining surfaces with living cells and this may represent a promising alternate path to the use of synthetic materials in contact with blood. Basic research is yielding further information about the changes which take place when blood interacts with natural and synthetic surfaces.

A family of polymers, segmented polyether-urethanes, has been developed which combines good mechanical performance with fairly good blood compatibility. These materials are currently being developed for use in circulatory assist devices. Other polymers, sulfonated polystyrenes, also exhibit promising blood compatibility. Polyalkylsulfones are other candidate materials which can be modified to suit a variety of end uses. Their blood compatibility has not been evaluated fully at this time. Other promising artificial materials are interpenetrating polymer networks with hydrophilic polymers and silicone elastomers which show good blood compatibility properties as well as high gas transfer rates for oxygen and carbon dioxide. These are being developed for use in artificial lungs (oxygenators).

One current study deals with the physicochemical and mechanical evaluation of a new class of so-called "springy" polypropylene which has a unique combination of properties for potential prosthetic applications. Preliminary results indicate that the material does not undergo mechanical changes during extended exposure to whole blood and is uniquely similar to certain tissues in its visco-elastic properties. The required blood compatibility may be imparted to this polymer by a variety of surface treatments.

Significant progress has been made in the development of new techniques to impart blood compatibility to otherwise noncompatible polymers. In particular, certain hydrogel materials have been successfully grafted by covalent bonding onto a variety of polymeric materials. Further refinement has been achieved in the process of ionic bonding of heparin (an anticoagulant) to polymeric substrates. This technique represents a practical tool for imparting short-range thromboresistance to some polymers, in particular silicone elastomers.

Improvements have been made in the test systems for assessing the blood compatibility of biomaterials. The best synthetic materials to date in terms of producing minimal blood changes are hydrogel-grafted surfaces and low-temperature isotropic carbons. Good results have also been obtained with certain segmented polyether-urethanes, mentioned earlier.

Further progress has been made in evaluating the long-range mechanical and physical performance of synthetic polymers in the biological environment. The absorption of blood components gives rise to highly significant changes which not only affect the mechanical performance of the material but also change its surface morphology and, hence, biological performance. Studies are in progress to establish the long-term bulk and surface characteristics of polymeric materials used for cardiac and pulmonary devices. The initial work has focused on certain segmented polyether-urethanes.

FUTURE CHALLENGES

Increased emphasis must be placed on the fundamental aspects of the interactions between blood and biomaterials. Improved biomaterials suitable for specific physiologic requirements need to be developed and improved techniques for modifying and grafting surfaces must be explored.

A better understanding of the mechanical and physicochemical properties of natural tissues needs to be developed so that this basic information can be used for the synthesis of new materials for specific biomedical applications. There is a tremendous future challenge in using the natural tissues as models to create synthetic systems with properties approximating those of the natural tissues. This applies not only to the blood/surface interactions (blood compatibility) but also to the entire physicochemical and mechanical performance of the system. The conformational changes which occur during the adsorption of blood proteins on biomaterials need further clarification. Better tests for blood compatibility are needed since the currently used test systems have relatively small surface areas and involve expensive animal work.

ACTIONS The Institute plans to:

1. Support basic research into interactions of blood components with both synthetic materials and natural biopolymers.

2. Explore the synthesis and preparation of a variety of biocompatible materials suitable for specific uses in medicine.

3. Develop improved methods for the physicochemical and biological evaluation and characterization of biomaterials.

SCHEDULE Expansion of the basic science aspects of this program and development of improved testing systems will occur during FY 75 and FY 76. The program should reach full strength by FY 78 by which time clinical trials will be underway.

4. BLOOD RESOURCES

The supply of blood and blood components is a critical national problem. Blood is a very important therapeutic tool. The demand for blood and blood fractions is increasing with no foreseeable limit except that dictated by the practical considerations of limited supply. In the face of an increasing demand and a limited supply of blood, it is important that economical and efficient use be made of the available blood resources. Critical national problems that need to be dealt with are: the current wastage of blood, the lack of uniformity of blood collected, and the lack of uniform criteria for usage.

The National Heart, Blood Vessel, Lung, and Blood Act of 1972 significantly expands the authority and responsibility of the Federal Government in areas which include the use of blood and blood products and the management of blood resources. The Act also requires the NHLI to develop a plan for research and educational activities related to implementation of a national blood policy. Such a plan was presented in the National Heart and Lung Institute Summary (Volume I) of the National Heart, Blood Vessel, Lung, and Blood Program on May 1, 1973.

The updated 5-year Plan in Blood Resources is presented here. Four program areas are discussed in this section: a Nationwide Blood System, Safety of Blood Therapy, Blood Component Therapy, and Transplantation Biology. These four areas are discussed in terms of their recent progress, future challenges, and actions. One Action, the development of Specialized Centers of Research, is applicable to all of the program areas. This Action, together with the schedule for the entire blood resources program, is discussed last under Overall Action and Overall Schedule. The program goals are also applicable to all program areas and are discussed first as Overall Program Goals.

Overall Program Goals

The present blood resources complex, while providing essential services and products, has not consistently maintained an adequate supply or achieved the highest attainable quality of blood therapy. The goals which the National Program recognizes in the provision of blood services to the people of the United States are to promote and maintain:

- Adequate blood supply
- Highest attainable quality
- Access to the supply for everyone in need
- Efficiency in the collection, processing, storage, and utilization of blood.

Nationwide Blood System

RECENT PROGRESS

The Institute continues to collaborate with the Office of the Secretary of the Department of Health, Education, and Welfare, the Bureau of Biologics of the Food and Drug Administration, and the private sector in order to foster the rapid implementation of a truly nationwide blood program. The Institute also continues to support research which will assist in the future implementation of a Blood Data Collection Center to supply comprehensive and continuous information on the supply, size, distribution, and use of blood and blood products. Development of a standardized cost-finding methodology for blood banks is in progress. Regionalization of blood supply systems is being investigated. Recently, the blood banking sector was charged by the Secretary of the Department of Health, Education, and Welfare to submit its plans for implementing the National Blood Policy. The Institute will consider these plans in determining future funding of research primarily aimed at fostering the implementation of a nationwide blood program.

FUTURE CHALLENGES

The present nationwide blood system is fragmented and poorly coordinated at a national level. The result is an inefficient use of resources and a compromise in quality. What is known often has been applied slowly. Despite these shortcomings, the blood service complex has enormous strengths and, in the main, has served the American people well.

The specific future challenge for both the National Heart and Lung Institute and other government and private agencies is to encourage the development of an appropriate mechanism for implementing cost-effective systems and regionalization. Other

important challenges are improved approaches to determine the utilization of blood and blood products for specific blood diseases and other clinical conditions and to assess their immediate and future impacts (e.g., projected expansion to supply new needs in coronary artery surgery) on the limited national blood resource.

ACTIONS

The Institute plans to:

1. Coordinate its efforts with private and public organizations involved in blood banking in the creation of an all-voluntary blood donation system and regional integration to increase effectiveness.

2. Assist in the implementation of a Federal Blood Data Collection Center, in cooperation with the Bureau of Biologics and the Department of Commerce, to provide comprehensive and continuous information and evaluation concerning the nation's blood supply, its size, distribution, and use.

SCHEDULE

See Overall Schedule at the end of this section.

Safety of Blood Therapy

RECENT PROGRESS

Three ad hoc committees have been established to coordinate extramural hepatitis research funded by government agencies or institutes. One of the committees supported a workshop on future work on hepatitis epidemiology. From this workshop, the National Heart and Lung Institute has developed its hepatitis epidemiology program.

A recently completed study indicates that hepatitis B immune globulin has no effect in the treatment of acute fulminant hepatitis. Technological improvements in the test for hepatitis carriers have made this assay more sensitive and specific. The chronic carrier state does not appear to be due to a generalized immunodeficiency and no specific deficiency has been found. The studies of the efficacy of hepatitis immune globulin in the prevention of hepatitis in high-risk patients are in progress and should yield important answers in this fiscal year.

Presently available data are inconclusive as to whether cytomegalovirus (CMV) infection results from transmission by transfused blood or by activation of latent virus in the recipient. A cooperative trial is presently underway to determine the clinical importance of blood transfusion in cytomegalovirus infection.

Fail-safe systems for donor-recipient identification have been developed and tested in limited but successful clinical trials at local hospitals. Within the coming year, three devices will each undergo extensive trial, and the most effective device will be identified.

The safety of transfused blood is also the underlying concern in studies of blood bag materials. Toxicology studies are underway on di-2-ethylhexylphthalate (DEHP), a substance present in blood bag materials. Current data show that DEHP is leached from blood bags and circulated to the patient's tissues during transfusion. The clinical importance of this finding is under investigation.

FUTURE CHALLENGES

In spite of rapid advances in the understanding of hepatitis, primarily serum hepatitis, there is still no way to ensure that blood from a given donor will not transmit this disease. Cytomegalovirus disease is also emerging as a common cause of death in transfused patients whose immune mechanisms are depressed. The role of the blood donor and/or the recipient in the transmission of cytomegalovirus must be elucidated and means of prevention developed and implemented. Human error in matching donor and recipient remains a major hazard in transfusion therapy and fail-safe systems need to be developed and applied.

Retransfusing the patient's own blood constitutes the safest form of transfusion therapy. Means must be explored to develop further this form of therapy, termed autotransfusion, both by having the patient bank his blood prior to need, and by returning to him blood lost during surgery. In addition to increasing safety, this form of therapy might be expected to reduce significantly the demand on the nation's blood resources.

The final test for hepatitis in blood may have to await the identification of new antigens or the development of an entirely new approach to testing, perhaps involving a bioassay method. Elimination of <u>any</u> chronic virus carrier state by some intervention technique is not possible at present. We are at present only able to define the carrier state without affecting its course.

The magnitude of the CMV problem remains to be determined. Should blood be conclusively proven as the primary mode of CMV transmission, a method to detect infectious blood applicable to mass screening would be needed to reduce the morbidity and mortality associated with CMV. Methods to prevent contamination and to remove the contaminating agent would also be explored.

Future challenges for fail-safe systems of donor-recipient identification on the national scale involve the general, large-scale acceptability of devices and the high cost of acquiring and maintaining them. The potential toxicity of plastics in contact with the blood needs further study.

ACTIONS

The Institute plans to:

1. Participate with other agencies in a concerted attack on hepatitis which will include development and use of more sensitive and practical tests for detecting carriers, studies of the carrier state, removal of hepatitis from blood and blood products, and development of methods for passive and active immunization.

2. Continue studies in the areas of toxicology of plastic devices having contact with blood, the evaluation of fail-safe donor-recipient identification systems, and studies which will identify the risk of cytomegalovirus infections caused by blood donors and/or recipients.

SCHEDULE

See Overall Schedule at the end of this section.

Blood Component Therapy

RECENT PROGRESS

Research is in progress to explore new methods of plasma fractionation to determine if the components presently being prepared can be recovered more efficiently and economically. Plans have been formulated to develop new fractionation products, and these efforts will be implemented shortly.

FUTURE CHALLENGES

The medical demand for red blood cells, as distinguished from other blood components, sets the pace for the collection of whole blood. Patients who need red cells often do not need other components. Currently, whole blood is used in more than three-fourths of all transfusions, although experts indicate that it is necessary in less than one-fourth of the cases. Reducing the use of whole blood not only constitutes good medical practice, but will increase the availability of components often in short supply and needed by other patients.

Specific research efforts are needed to improve methods for storing blood cells, for collecting blood, for maintaining viability and function of platelets and white blood cells, and for improving methods of fractionating blood into its various components. These efforts will require a dynamic cooperative program which will involve other government agencies as well as the private sector.

ACTIONS

The Institute plans to:

1. Support and participate actively with other interested organizations to insure that new fractionation methods are devised and/or supported which would cope with the ever increasing demands being placed on blood resources, to assure adequate amounts of coagulation factors, particularly Factor VIII for hemophilia.

2. Develop means to enhance and evaluate the appropriateness of blood utilization through clearer indications for the use of blood components and better methods to assess their effectiveness.

3. Implement the US-USSR cooperative program on blood transfusion, particularly in relation to cardiovascular surgery.

SCHEDULE See Overall Schedule at the end of this section.

Transplantation Biology

RECENT PROGRESS Investigators are actively pursuing means to prevent the sensitization of the transplant patient by lowering or eliminating histocompatibility antigens (HL-A) in transfused blood, and studies are underway to determine the indications for HL-A typing in platelet transfusions. Current studies of in vitro methods for removing histocompatibility antigens will be followed by clinical trials on renal dialysis patients to determine if sensitization to HL-A antigens can be reduced or prevented.

Many methods of removing histocompatibility antigens from blood have been studied. Freezing blood appears to destroy histocompatibility antigens with maximum preservation of red cells, but cost factors and the lack of freezing facilities at most institutions limit the present utility. Another method of removing histocompatibility antigens by a double centrifugation process is relatively simple and appears promising. The clinical studies have demonstrated trends which indicate more rapid sensitization in preparations with intact leukocytes and platelets but statistically significant results have not yet been obtained.

FUTURE CHALLENGES In addition to handling blood, a nationwide blood system may also be responsible for the preservation, storage, and typing of tissues and organs for transplantation. Fundamental knowledge in transplantation biology will be necessary before transplantation can be used more widely and more successfully. Studies of the prevention of graft-versus-host reactions, the development of better immunosuppressive techniques, and the prevention and treatment of infection will be undertaken.

The development of organ preservation devices is required before a system of regional or national organ procurement is feasible. The design and development of such devices will have to follow extensive fundamental research in organ preservation so that the factors relevant to successful preservation can be included in the design of devices.

ACTIONS

The Institute plans to:

1. Encourage fundamental research (in conjunction with other Institutes) in immunology, immunogenetics, and other aspects of transplantation biology.

2. Initiate clinical studies (in conjunction with other Institutes) to improve the management of the post-transplant state, such as prevention of graft-versus-host reaction, the development of better immunosuppressive techniques, and the prevention and treatment of infection.

3. Implement studies to improve organ preservation and procurement.

SCHEDULE

See Overall Schedule below.

Overall Action

Applicable to all of the above blood diseases and blood resource problems are Specialized Centers of Research. The Institute plans to:

1. Establish one or two Specialized Centers of Research in Blood Diseases and Blood Resources. These Centers could emphasize improved blood therapy using cellular components, particularly white cells and platelets, and plasma components including those used in treatment of hemophilia, and may contain pilot plants to test new methods developed for plasma fractionation.

Overall Schedule

Increased activities relating to the National Blood Policy are expected in FY 75 and FY 76. The hepatitis program will expand through FY 77 at which time peak funding will be reached. Research in Transplantation Biology will double by FY 77 and expand gradually through FY 79. A Center in Blood Resources will be established in FY 75.

PREVENTION, CONTROL, AND EDUCATION

Prevention, rather than treatment, of heart, blood vessel, lung, and blood diseases offers the greatest promise of reducing death and disability in the United States. More effective application of existing knowledge will materially reduce disability and death from the complications of these diseases. The Institute has provided for expanded future emphasis on bridging the gap between research findings and clinical applications by establishing an Office of Prevention, Control, and Education. An Assistant Director for Health Information has been recruited from within the Institute. This position is mandated by Section 413(d) of Public Law 92-423. The function of this office will be to expand and coordinate the various NHLI programs directed toward the goals set forth in this section of the Plan. Identification of priority areas is already underway. The National High Blood Pressure Education Program (see below) was initiated in 1972 and will serve as a model for other education programs identified as high priority and launched in the future. Through the study of the impact of the various segments of the High Blood Pressure Education Program, and consultation with authorities in educational technology and motivational analysis, the Institute has begun planning for a more effective national program in public and professional information and education designed to implement five overall Actions in the Plan.

Overall Actions

1. Develop education programs for each of the categorical program areas of the Institute.

2. Develop better mechanisms, using all media of communication, to disseminate knowledge about heart, blood vessel, lung, and blood diseases and blood resources.

3. Establish improved means for direct communication with the public.

4. Expand programs to aid health professionals in improving the public's understanding and application of new health knowledge and concepts.

5. Establish improved means for communication with the scientific community and the medical profession.

The overall goal of the Prevention, Control, and Education Programs of the Institute is to hasten the control and, in the long run, to prevent or lower the prevalence of cardiovascular, pulmonary, and blood diseases in the population. The emphasis will be on prevention of disease, but in order to achieve optimal success, it will often be necessary to aid the existing health care delivery system in detection of individuals at high risk for a variety of diseases. Improved detection will depend in part on increasing the level of awareness within the population about risk factors, how to enter

the health care system, and the importance of patient adherence to management regimens once diagnosis has been established. The educational components of the Institute's control programs will receive the highest priority.

Professional education and rapid dissemination of research knowledge from clinical investigation will be stressed to control disease. Education and use of paraprofessionals in community efforts toward control and prevention of disease will be stimulated. The concept of health care delivery team approaches, including team members specializing in patient education, is gaining rapid acceptance. Although categorical disease approaches to education, prevention, and control will be used, the Institute will attempt to coordinate and give highest priority to those programs which can serve as models for application to other diseases.

As resources become available, NHLI intends to provide funding for local and regional demonstration programs of prevention, control, and education which embrace the above principles. These programs must involve the several components of the health care system within a given geographical area, although they may be primarily based in medical schools or major medical centers. In order to be maximally effective, funding of these programs will need to insure a reasonable degree of long-term, stable support. As stated earlier, these programs are not intended to fund health care delivery *per se*, but rather to help effect the transmission of fundamental research advances to the public. The manpower necessary for coordination, provision of educational opportunities, and preparation and dissemination of educational or informational material will require support. These programs will be funded on the basis of merit as determined by national competition.

Shorter-term demonstration projects are also envisioned as part of the Institute's programs. These demonstration projects will deal with specific techniques (e.g., methods of detection) which are not currently accepted or commonly in use for disease control. The intent of a demonstration project should be to provide clear evidence that the new technique is applicable to a community situation, does not overload the existing health care system, is cost-effective, and results in an improved ability of the local health care system to respond to the need which the new technique addresses. Once the demonstration project has confirmed the feasibility of its approach, NHLI funding will be discontinued. Results will be made available to the medical community at large by description in national publications, through National Research and Demonstration Centers, and through voluntary and other health organizations. Staff from NHLI and from the demonstration projects themselves will be available as consultants to other communities who wish to adopt the technique to their own needs. Other examples of demonstration projects might be new approaches to continuing education of physicians in cardiovascular and pulmonary subjects, an improved system of assessing patient compliance with antihypertensive regimens, or a rapid method for on-site diagnosis and treatment of dangerous arrhythmias.

In order to be maximally responsive to available opportunities, both the grant and contract mechanisms should be available for funding of the time-limited demonstration projects and the longer-term programs for prevention, control, and education. Applicants should be able to seek support on a regular basis for ideas in these program areas, either by the grant mechanism or by unsolicited proposals for contract support. In addition to such projects, the Institute plans to support demonstrations solicited through program announcements for support of projects or programs of high priority under the 5-Year National Plan.

For FY 75, the highest priority program areas are hypertension, arteriosclerosis, inhalation lung diseases, and sickle cell disease, in which modest funds are currently available for educational programs. In addition, as resources become available, new efforts need to be directed to cardiac rehabilitation and emergency cardiac medical services, nutrition and coronary artery disease risk factors, early diagnosis (including prenatal diagnosis) of respiratory distress syndrome in the newborn, emergency treatment of respiratory failure secondary to severe trauma, smoking as a risk factor, and improved approaches to blood component therapy. Specific plans relating to heart and blood vessel, lung, and blood disease and blood resource programs are summarized below.

HEART AND BLOOD VESSEL DISEASES

Considerable knowledge is already available on the prevention and control of heart and blood vessel diseases. However, achieving the most effective means for applying this knowledge to individuals in need requires more specific research and evaluation efforts. The prevention and control programs, therefore, seek immediate application of presently available knowledge for prevention and control and at the same time strive to make prevention and control measures more effective.

Particular emphasis will be placed on the testing and evaluation of a program for the prevention of the two major cardiovascular disorders--hypertension and arteriosclerosis. For these two disorders, a sufficient base of knowledge exists which could effect substantial reductions in morbidity and mortality if the knowledge were implemented through coordinated and comprehensive programs. Prevention or amelioration of other cardiovascular disorders requires attention in implementing the National Program. Specific programs for hypertension, arteriosclerosis, coronary heart disease, and congenital heart disease are discussed in this section. The activities described under hypertension and arteriosclerosis are continuations of activities already underway. The activities described under coronary heart disease and congenital heart disease are new, planned initiatives.

1. HYPERTENSION

PROGRAM GOALS

Drug therapy to control blood pressure reduces the incidence of strokes and heart failure among persons with moderate and severe hypertension. However, only about 12 percent of hypertensives are currently receiving adequate treatment. Immediate efforts to expand current program initiatives through existing medical networks are urgently needed to bring individuals with moderate and severe hypertension under effective treatment. Sustained effective blood pressure management in such persons should result in a reduction of disability and death by as much as 40 percent when compared with expected rates for untreated hypertension.

- A national goal of the program is to motivate all adults to have their blood pressure checked annually and for those found to be hypertensive, to urge them to obtain proper therapy.

- Another national goal is to make current knowledge of antihypertensive drug management available to and effectively practiced by the general practitioners as well as the specialists from whom the individuals with high blood pressure seek proper therapy.

RECENT PROGRESS

The National High Blood Pressure Education Program, initiated in 1972, has completed the preliminary studies of the needs of the program, and the Hypertension Information and Education Advisory Committee has submitted its recommendations to the Secretary, Department of Health, Education, and Welfare. Implementation of some recommendations addressed to immediately recognizable needs is being planned or has already been initiated.

In the Hypertension Detection and Follow-up Program, over 10,000 hypertensive patients from 14 communities of all races and several ethnic groups, and both men and women, are being invited to participate in a treatment program. Over one-third of the participants will be black and include both rural and inner city residents. Special educational efforts are being undertaken to encourage patients to attend clinics and to take their medication regularly.

FUTURE CHALLENGES

Important challenges in prevention and control of high blood pressure include the development of simplified medical regimens using available antihypertensive drugs and the creation of systems which will optimize the utilization of nurses and allied health professionals in educational and therapeutic programs under physicians' supervision. The problem of motivating patients to take and adhere to long-term antihypertensive drug therapy requires

further research. The use of demonstration programs which seek effective implementation of hypertension detection, diagnosis, treatment, and follow-up systems in the community in cooperation with existing medical and community health resources, needs to be explored.

ACTIONS

The Institute plans to:

1. Continue the Hypertension Information and Education Program to expand public and professional knowledge of the dangers of high blood pressure and the benefits of effective treatment.

2. Establish an education research program aimed at testing hypotheses that will lead to new knowledge in methods of education that will (a) increase awareness of the problem; (b) define cost-effective methods of delivering patient care and patient education, and/or (c) identify methods of increasing patient compliance.

3. Continue a Hypertension Detection and Follow-up Program to determine the effectiveness of a systematic approach using antihypertensive therapy in reducing mortality among those with elevated blood pressure in community-based populations.

SCHEDULE

The NHLI's current activity in this area will be continued with increased emphasis over the next two years and receive sustained support thereafter.

2. ARTERIOSCLEROSIS

PROGRAM GOALS

A number of factors that increase susceptibility to atherosclerosis and coronary heart disease have been identified. These include elevated blood lipids, high blood pressure, and cigarette smoking. These risk factors can be modified and the public needs to know how this can be done.

- The program goal is to reduce disability and death from arteriosclerotic disease of the blood vessels to the heart, brain, and extremities through the prevention and control of risk factors.

RECENT PROGRESS

A working group drawn from the National Heart and Lung Institute, United States Department of Agriculture (USDA), and Food and Drug Administration (FDA) has been established and has met several times. The interests, plans, and priorities of these three agencies

with regard to prevention and control of hypertension have been explored. The FDA's new voluntary food labeling regulations and the USDA's planned nutrient data bank (which has been approved by the food industry) will eventually make available a wealth of nutrition information.

The National Heart and Lung Institute helps to support certain studies by the USDA's Consumer and Food Economic Institute of the Agriculture Research Service. These include a literature search and documentation and identification of the nutrient composition of foods.

A continuing dialogue between these three government agencies is underway. A long-term objective is to evaluate the need for a national food analysis laboratory to complement the USDA's planned nutrient data bank.

The nutritional support staffs of both the Multiple Risk Factor Intervention Trial (MRFIT) and Lipid Research Clinic (LRC) trials (see section on Arteriosclerosis under Research) have been actively interacting with university groups and the American Heart Association to explore all available avenues for promoting nutrition education. Although the development of education materials and techniques appropriate for the MRFIT and LRC trials is the immediate goal, such material and methods will eventually find more general use. General interest in nutrition and heart disease has increased throughout the country. The Institute has become increasingly involved in professional education programs sponsored by voluntary and official agencies. The NHLI has also revised its informational series on the dietary management of hyperlipoproteinemia. These revised diet manuals are available for physicians and nutritionists.

FUTURE CHALLENGES

It is now possible to identify persons who may be at increased risk of developing coronary heart disease, stroke, or peripheral vascular disease by measuring their blood lipids, blood glucose, blood pressure, and weight, and by obtaining information on cigarette smoking. An electrocardiogram further improves the prediction of risk.

Using these factors as indicators, we can identify the 20 percent of the population who are most likely to develop 40 percent of the coronary heart attacks, 50 percent of the strokes, and 50 percent of the clinical peripheral vascular events over a subsequent six-year period. This is not an absolute because heart attacks, strokes, and peripheral vascular disease also occur in persons without such risk factors. However, the highest priority should be given to identification of these high-risk susceptible individuals by relatively simple procedures.

Once susceptible individuals have been identified, measures can be initiated to reduce their risk status through dietary measures, drugs for lowering lipids or blood pressure, and modification of life styles. This is a difficult task and how to achieve such changes in an acceptable manner for large segments of the population remains to be determined.

ACTIONS

The Institute plans to:

1. Cooperate with the Department of Agriculture and other Federal agencies having a nutrition-related interest to establish policies and education programs on the role of nutrition in heart disease; develop, evaluate, and apply dietary survey and counseling methods in the treatment of hyperlipidemia.

2. Support, in cooperation with the Department of Agriculture and the Food and Drug Administration, a special program to update the information on composition of foods in the American marketplace.

SCHEDULE

The Information Program for risk factor detection and prevention will be increased in FY 76 and receive sustained support thereafter. It is projected that support for nutrition programs will increase substantially in FY 75 and increase incrementally thereafter.

3. CORONARY HEART DISEASE

PROGRAM GOALS

As discussed in the Research section on Coronary Heart Disease, emergency medical care for the person with suspected heart attack is a major problem, since there are about 400,000 deaths annually from coronary heart disease prior to hospitalization.

- A goal of this control program is to introduce the developments in emergency medical care for the cardiac patient into comprehensive emergency care systems.

- An additional goal is to conduct research on improved methods for rehabilitation.

RECENT PROGRESS

The Institute has been supporting research actions to develop information for the design and evaluation of emergency care systems and is participating with other agencies in an Interdepartmental Committee on Emergency Medical Services.

The NHLI has convened a task force to study the present state of our knowledge as it relates to cardiac rehabilitation. Recommendations will be developed for clinical implementation of what is known and practical, and for initiating effective research where necessary.

FUTURE CHALLENGES

A saving in lives and probably a decrease in disability from heart attacks can be achieved by improved emergency medical systems for the cardiac patient. In addition, once a heart attack or other serious cardiac illness has occurred, the rate and completeness of return toward normal functioning in society and enjoyment of life remain inadequate. Present studies indicate that disability can be minimized and recovery hastened by appropriate attention to the medical and psychological factors associated with cardiac rehabilitation. However, the optimal, practical methods for achieving such rehabilitation need to be developed, assessed, and demonstrated.

ACTIONS

The Institute plans to:

1. Contribute, in collaboration with other Federal agencies, to the design and analysis of the cardiac elements of emergency care systems. Such programs will emphasize the implementation of research developments under Actions in the Research section on Coronary Heart Disease.

2. Explore, in collaboration with the Social and Rehabilitation Service, the establishment of demonstration programs for the rehabilitation of patients with cardiovascular disease.

SCHEDULE

The schedule for the first Action is contingent upon scheduling of the comprehensive Emergency Medical System; NHLI components could be initiated in FY 75 and continued through FY 78. Collaborative efforts on rehabilitation programs were initiated in FY 74 and will be continued through FY 80.

4. CONGENITAL HEART DISEASE

PROGRAM GOALS

Recognition of congenital heart disease is particularly difficult during the newborn period. Yet this is the period during which a substantial fraction of deaths from congenital heart disease occurs.

- The goal of this control program is to recognize and manage congenital heart disease in the newborn.

RECENT PROGRESS

New investigations and the development of a variety of diagnostic techniques are providing capabilities for more ready and accurate assessment of congenital heart disease. Also, there has been an increased understanding of the pathophysiology of the disease processes and their symptoms. These new developments are being combined to allow for better and earlier recognition of congenital heart disease in the neonate by nursery staff and physicians. For example, new investigations recently begun in the field of ultrasonic imaging by acoustical holography provide a new capability for examining the anatomy of a newborn child in the manner of low resolution X-ray fluoroscopy, but without the use of X-rays. Thus, normal and abnormal anatomical structures and physiologic functions (e.g., movement of joints, flow of blood in specific vessels, operation of heart valves) can be visualized directly in a way believed to be nonhazardous to the infant. The nontraumatic nature of the method has resulted in rapidly increasing application of ultrasonic imaging examinations to large numbers of pregnant women in the United States and abroad.

FUTURE CHALLENGES

A substantial saving in lives can probably be achieved by early recognition of cardiac problems in the newborn and the establishment of specialized groups to deal with these problems.

ACTIONS

The Institute plans to:

1. Explore the feasibility of demonstration programs for the early recognition of cardiac (and respiratory) problems in the newborn. Such programs will emphasize intensive professional education, development of instrumentation for improved detection, better interhospital communication and transport, and the availability of diagnostic and surgical facilities for treating critically ill infants.

SCHEDULE

The program will be initiated in FY 76 and continue through FY 80.

LUNG DISEASES

The major emphasis in prevention, control, and education in the lung diseases area will focus on control programs in inhalation diseases. Other efforts include programs in fibrotic and immunologic lung diseases, pediatric pulmonary diseases, respiratory failure, and smoking in emphysema and chronic bronchitis.

1. INHALATION DISEASES

PROGRAM GOALS

This new program area is directed toward preventing or treating inhalation diseases by removal of the offending substance or by protecting individuals against exposure to them.

- A primary goal is to disseminate information about the types of dusts, vapors, and gases that can cause inhalation diseases and how to avoid them.

RECENT PROGRESS

Improved standards in terms of exposure levels have been developed for asbestos-related industries. Anticipated in the future are improved and safer standards for silica as well.

FUTURE CHALLENGES

A great deal is already known to the scientific community about the types of environmental agents associated with industries and occupations. It is essential that this information be widely disseminated to community physicians and the lay public.

ACTIONS

The Institute plans to:

1. Develop a program of education for physicians and the lay public with regard to inhalation diseases. This will be accomplished through workshops for physicians, literature for the public, and control programs addressed to avoidance of noxious dust, vapors, or gases.

SCHEDULE

This new activity was initiated in FY 74 and will undergo incremental increases through FY 80.

2. FIBROTIC AND IMMUNOLOGIC LUNG DISEASES

PROGRAM GOALS

Fibrotic and immunologic lung diseases are induced by external agents and can be prevented or treated by removal of these agents or suppression of their effects.

- A primary program goal is to disseminate information about the causes of fibrotic and immunologic lung diseases and how to avoid them.

RECENT PROGRESS

A symposium, oriented toward fibrotic and inflammatory lung diseases, was held during a recent New York Academy of Science meeting. This symposium, attended by general physicians as well as researchers in the field, was important in encouraging the exchange of information necessary for preventing these diseases.

FUTURE CHALLENGES

Available knowledge about external agents implicated in the development of immunologic and fibrotic lung diseases needs to be widely disseminated to the lay public as well as to physicians. This is

essential to prevention of these diseases. Specific future challenges for the Institute include the organization of meetings and workshops for the public and general practitioners, and the preparation of literature for dissemination.

ACTIONS

The Institute plans to:

1. Develop a program of education of physicians and the lay public with regard to environmental agents implicated in pulmonary fibrosis and immunologic lung diseases. This will be accomplished through workshops for physicians, literature for the public, and control programs addressed to avoidance of etiologic agents in the community.

SCHEDULE

The program in education regarding fibrotic and immunologic lung diseases will increase incrementally from FY 76 to FY 80.

3. PEDIATRIC PULMONARY DISEASES

PROGRAM GOALS

About 50,000 babies are born each year with hyaline membrane disease. More than half of these will die unless given prompt treatment. Research programs in pediatric pulmonary diseases are focused upon the development of more effective diagnostic and therapeutic methods. Until sufficient knowledge is gained about prevention of hyaline membrane disease, the only hope for these patients lies in prompt diagnosis and treatment.

- The primary goal will be to initiate prompt diagnosis and therapy of hyaline membrane disease.

RECENT PROGRESS

While specific demonstrations have not been initiated, research results with respect to continuous positive pressure ventilation and early diagnosis have been disseminated through journals and at meetings. In addition, a workshop on pediatric pulmonary disease has been held and a report disseminated to the pulmonary community.

FUTURE CHALLENGES

In order to initiate prompt diagnosis and therapy, available information about pediatric pulmonary disease needs to be disseminated to appropriate forums in a meaningful way. The major challenge in this area is to improve communication between the Institute and the pulmonary biomedical community.

ACTIONS

The Institute plans to:

1. Develop education programs, addressed to pulmonary and community physicians, to provide presently available information about treatment of hyaline membrane disease. This will be done through demonstration projects and workshops.

SCHEDULE

These education programs will be phased-in subsequent to the steadily increasing activities in therapy described under the Research sections on Pediatric Pulmonary Diseases and Structure and Function of the Lung. They will thus be able to capitalize on information accruing from other new actions.

4. RESPIRATORY FAILURE

PROGRAM GOALS

Considerable progress has been made in the development of therapy, but unless treatment is initiated promptly by experienced personnel, respiratory failure will lead to death in more than half of those affected.

- The first goal of the program in this area is to disseminate the knowledge needed to save lives through early recognition and treatment of respiratory failure.

RECENT PROGRESS

The information available on hyaline membrane disease is being applied in several medical centers, resulting in significant decreases in infant mortality rates. To improve and evaluate the effectiveness of continuous positive airway pressure as primary treatment in many cases of severe respiratory distress syndrome, several groups of investigators are using common criteria for diagnosis of the syndrome and for initiation and termination of the treatment.

Two groups are now working on adult positive ventilation techniques in intensive care units, and further improvement and dissemination of this and other recently developed procedures are anticipated.

FUTURE CHALLENGES

Available knowledge about detection and treatment of respiratory failure needs to be widely disseminated to community physicians and allied health personnel, as well as to pulmonary physicians. Specific future challenges are to increase the number of centers participating in the treatment of infant and adult respiratory distress and to simplify the procedures and equipment so that smaller hospital units, as well as the larger centers, may apply this knowledge.

ACTIONS

The Institute plans to:

1. Initiate demonstration projects in which available information will be widely disseminated to educate pulmonary and community physicians and allied health personnel in what is known about respiratory failure.

SCHEDULE

The major new activity will be demonstration programs. Educational activity will undergo a delayed increase, capitalizing on new information accruing from treatment studies.

5. EMPHYSEMA AND CHRONIC BRONCHITIS

PROGRAM GOALS

Cigarette smoking is believed to be a prime factor in the etiology or exacerbation of chronic bronchitis and emphysema, and a contributing factor to environmental lung diseases, including the pneumoconioses and hypersensitivity lung diseases. Up to 20 percent of smokers have chronic obstructive lung disease and almost all patients with this disease are smokers. Extensive studies document conclusively that cigarette smokers are far more likely to develop emphysema than nonsmokers. Also, once developed, emphysema progresses much more swiftly in those who smoke. Repeated exposure to pollutants in the air also contributes to the development and progression of the disease.

The principal cause of chronic bronchitis is prolonged irritation of the bronchial tube linings. Smoking, air pollution, and recurrent infections are the main irritants for chronic bronchitis, as well as for emphysema. The public needs to be informed about the potential seriousness of persistent or recurrent coughs and shortness of breath and about ways to protect against progression of these diseases.

- The program goal is to modify the smoking habits of persons at risk of developing lung diseases, and to extend successful anti-smoking programs to the general population.

RECENT PROGRESS

The difficulties in modifying human behavior are well-recognized. To achieve the stated program goal, research is urgently needed on the behavioral aspects of smoking. Institute Actions in support of such research are discussed in the section on Research programs.

In instituting an educational program on emphysema and chronic bronchitis for the lay public, NHLI has issued information pamphlets for the public and has informed community physicians of its programs at a recent meeting of the American Lung Association.

Research programs designed to promote early detection of emphysema and chronic bronchitis should ultimately provide a basis for intervention and/or prevention. In addition, environmental risk factors are being identified, which will provide a necessary first step toward prevention.

FUTURE CHALLENGES

A first step is the identification of persons at risk of developing chronic obstructive pulmonary disease, especially those individuals who are predisposed because of genetic characteristics. When populations have been identified, education programs effective in preventing smoking will need to be devised. The difficulty of motivating people not to smoke is well-known and presents a major challenge for the future. Sophisticated motivation approaches must be developed in cooperation with behavioral scientists to modify the smoking habits of persons at risk and, in general, large population groups. Those who have not yet acquired the habit should be discouraged from doing so through effective educational programs.

We also need to prevent or modify smoking in persons who live or work in environments with unusually high concentrations of air pollutants, dusts, or other environmental agents implicated in the development of lung diseases.

ACTIONS

The Institute plans to:

1. Develop a program, in collaboration with experts from other Federal agencies, to modify effectively the habits of smokers.

2. Develop an education program to alert the lay public to the dangers of smoking in relation to chronic obstructive pulmonary diseases and environmental lung diseases, and urge smokers in populations at special risk to participate in programs to modify their smoking habits.

These programs on smoking will be developed in collaboration with scientists concerned with the harmful effects of smoking on the cardiovascular system as well.

SCHEDULE

Behavioral and educational programs will be initiated in FY 75 to continue for five years.

BLOOD DISEASES AND BLOOD RESOURCES

Blood diseases and blood resources, as discussed in the Research section, are closely interrelated with heart, blood vessel, and lung diseases, and are important and integral parts of the National Program. Major prevention, control, and education programs in these areas are addressed to Sickle Cell Anemia and Cooley's

Anemia. These programs will emphasize education of the public, screening, and counseling. The NHLI is also supporting other programs in blood diseases and blood resources which focus on hemophilia, thromboembolic disease, and education about the nation's blood resources, control of hepatitis, and various aspects of organ transplantation. All of these programs are discussed below.

1. SICKLE CELL ANEMIA AND COOLEY'S ANEMIA

PROGRAM GOALS

Despite the fact that much is known about sickle cell disease and Cooley's anemia, the general public, including actual and potential victims, have a poor understanding of these disorders and their significance. Both diseases can cause great suffering. It is estimated that somewhat less than 50,000 Americans suffer painful episodes, or "crises," due to sickle cell disease, and at least 5,000 Americans suffer the effects of Cooley's anemia and require repeated blood transfusions in order to survive. In both cases, the diseases are transmitted by carriers to their offspring, if both parents carry the trait. Thus, education and control programs are important to the prevention of these diseases. The Institute is developing a program to expand community education to increase public awareness of these diseases and to educate these individuals.

- The goals of the control program are to inform the public about sickle cell disease and Cooley's anemia and to demonstrate techniques for appropriate screening and counseling.

RECENT PROGRESS

Programs are being developed to further expand the dissemination of information on sickle cell disease, utilizing nongovernment participation. Continuing education programs are being provided for physicians and paramedical personnel to emphasize established approaches as well as new developments in sickle cell disease through the programs in the Comprehensive Sickle Cell Disease Centers. Standardized techniques of screening (electrophoresis followed by confirmatory solubility) are being incorporated into comprehensive screening programs.

FUTURE CHALLENGES

We need to determine the prevalence and distribution of sickle cell disease and Cooley's anemia in this country, particularly the prevalence of carriers of the trait; provide accurate and up-to-date information on these diseases; initiate and expand appropriate community education, screening, and counseling programs; educate the medical and allied health professions about the problems of these diseases; identify and provide guidance for the management of the resulting psychological, sociological, and economic problems; and assist individuals with these disorders to attain their maximum potential in life.

ACTIONS

The Institute plans to:

1. Develop, in collaboration with other Federal agencies, programs to provide accurate information on sickle cell disease and Cooley's anemia; education for the general public, population groups at risk, health professionals, allied health professionals, educators, employers, and insurers of individuals who have these disorders; methods to best counsel affected individuals; and proper rehabilitation approaches when applicable.

2. Evaluate clinical approaches for the treatment of these disorders and other developments in the field and insure that the ones that are effective are incorporated into the health delivery system.

SCHEDULE

Screening and Education Clinics for sickle cell disease will continue to be heavily supported in FY 75. Information and education programs on both sickle cell disease and Cooley's anemia will be supported in FY 75 with a gradual reduction of activity from FY 76 to FY 80.

2. HEMOPHILIA

PROGRAM GOALS

Public awareness is fundamental to management and prevention of hemophilia. Although severe hemophilia affects only a known population of 25,000 in this country, it is a major national health problem. Treatment is very costly and must be continued throughout the patient's lifetime, thus demanding a large fraction of the nation's blood resources. Since the disease is hereditary, education of the public can be instrumental in its prevention.

- The goal of this prevention program is to educate the patient, the physician, and the general public so that patients with hemophilia and their families may make informed decisions regarding their own lives.

RECENT PROGRESS

There are no current education efforts in this area. The Institute is cooperating with the National Hemophilia Foundation and other national organizations to develop programs for the future. A Center for Blood Disease is in the planning stages and methods of education and counseling for hemophilia may be studied through this mechanism.

FUTURE CHALLENGES

The NHLI plans to study methods of genetic counseling and its impact on the hemophilia community, techniques of "total care" for hemophiliacs, and methods of minimizing the cost of hemophilia care for

the patient. Plans will also be developed for education programs directed toward the affected individual, the individual's family, the medical profession, and the general public. These efforts will be coordinated with those of the National Hemophilia Foundation.

ACTIONS

The Institute plans to:

1. Explore, in cooperation with other agencies, information, education, and genetic counseling techniques aimed at improving hemophilia therapy and preventing hemophilia.

SCHEDULE

Information, education, and approaches to genetic counseling in hemophilia will receive increased support in FY 76 and FY 77.

3. THROMBOEMBOLIC DISEASE

PROGRAM GOALS

Thromboembolic disease causes or contributes to a great variety of diseases in all parts of the body, including heart attacks, kidney failure, stroke, pulmonary embolism, and disorders of the microcirculation. Key to the prevention and control of thromboembolic disease is the identification of persons who may be at risk. Several risk factors associated with high risk for thromboembolic disease are known and it is now possible to identify those persons who may be at increased risk of stroke, pulmonary embolism, and thrombophlebitis and to take steps to prevent these disorders.

- The major program goal is to reduce disability and death from thromboembolic disorders by prevention and control of risk factors.

RECENT PROGRESS

Added emphasis is currently being placed on this program. International congresses on thrombosis and hemostasis were held in 1972 and 1973 and have provided a forum for discussion of thrombosis as a major world health problem and as part of a planned attack on this problem. Another more modest conference focused on clot-stabilizing enzymes and a workshop was conducted to review existing knowledge about the relationship of thrombosis to the development of myocardial infarction.

FUTURE CHALLENGES

Because rapid communication is important for advance in thrombosis and related fields, conferences on timely topics are planned to disseminate information as it is developed through research.

ACTIONS

The Institute plans to:

1. Explore, in coordination with other agencies, techniques for educating the medical community and the general public about risk factors and preventive measures in thromboembolic disease.

SCHEDULE

This program was initiated at a modest level in FY 74 and will be receiving gradually increased emphasis through FY 80.

4. BLOOD RESOURCES

PROGRAM GOALS

An adequate supply of blood resources is vital to the treatment, prevention, and control of many major diseases, including the ones addressed by the National Program. Not only must there be adequate supply of these resources, but they must also be of high quality in order to provide effective treatment and to avoid transmission of disease, such as hepatitis. Currently, neither adequate supply nor high quality blood is fully assured by the nation's operating blood service complex. Whole blood and blood components are collected by this complex and distributed throughout the nation. Special efforts are needed to assess the problems involved and to encourage more effective and economic utilization of these resources. A continuing program must be carried out for professional and public information and education about blood resources and the use of effective blood management systems. This is especially true of blood component therapy.

- The goal of this program is to achieve better management of the nation's blood resources.

RECENT PROGRESS

Two types of education efforts are being developed: (1) Education of technical/medical professionals to assure that whole blood is separated into its component parts and that the components are appropriately stored and made available to users; and (2) Efforts to influence the demand sector of the blood banking complex regarding optimal use of blood components in order to moderate the demand on the nation's blood resources.

FUTURE CHALLENGES

We need to develop ways to educate physicians regarding optimal use of blood components in order to moderate their demands on the nation's blood resources. The target population for the technical education efforts is the regional component of the coordinated nationwide blood system which is currently evolving in the United States. To stimulate optimal use of blood, attention will be directed at hospital blood banks and, at least initially, selected

populations of physicians, in particular, surgeons and anesthesiologists. Efforts also need to be made to evaluate the impact of the hepatitis program on the nation's health and to bring the results to the practicing physician, blood banker, high risk individual, and the general public.

The NHLI also plans to assess the psychologic, sociologic, and economic aspects of organ donation and transplantation. Motivation for organ donation and regionalization of "organ banks" will be investigated and evaluated in concert with the National Blood Program.

ACTIONS

The Institute plans to:

1. Support efforts to educate and influence physicians regarding optimal use of blood components and autotransfusion in order to moderate demands on the nation's blood resources.

2. Develop a coordinated program for hepatitis epidemiology and control.

3. Encourage efforts to develop a system of organ procurement on a regional and national basis.

4. Promote public dialogue on the ethical and legal problems associated with organ transplantation.

SCHEDULE

The Institute's efforts in education programs in blood therapy will be increased gradually over the next five years.

IV. PROGRAM COORDINATION

IV. PROGRAM COORDINATION

The National Heart, Blood Vessel, Lung, and Blood Program is designed to use national resources to attain the national long-term goal of improving the health of the American people. The achievement of a truly National Program remains a major challenge to the Institute. While we must not belittle the many real problems that remain in terms of National Program coordination, the Institute has made considerable progress in mobilizing interest in the Program. Through the National Program, the NHLI has a great opportunity to stimulate collaborative efforts at all levels and with all sectors of our society. In this manner the resources and direct efforts of the Institute have a multiplier effect far beyond what has been previously possible.

The Institute has, in the past, participated in many key collaborative efforts with other organizations throughout the nation. Such collaboration will continue to be expanded. During the planning stages of the National Program, both public and private sectors were called upon for inputs. These inputs to the Program, as detailed in the National Heart and Lung Institute Summary (Volume I, dated May 1, 1973), include other Bureaus, Divisions, and Institutes of the National Institutes of Health, other Federal agencies, and private, non-Federal and voluntary organizations.

In implementing the Program, this Institute continues to serve as the principal coordinator of a management system depicted in Volume I and reprinted here (Figure 1). As the focal point, the Institute can:

- Promote coordination of research and prevention, control, and education activities with many other organizations
- Assess the ordered sequence of program activities from basic research to demonstration in the community
- Evaluate the overall National Program in terms of ongoing and projected activities
- Gauge the impact of the Program on the health of the American people.

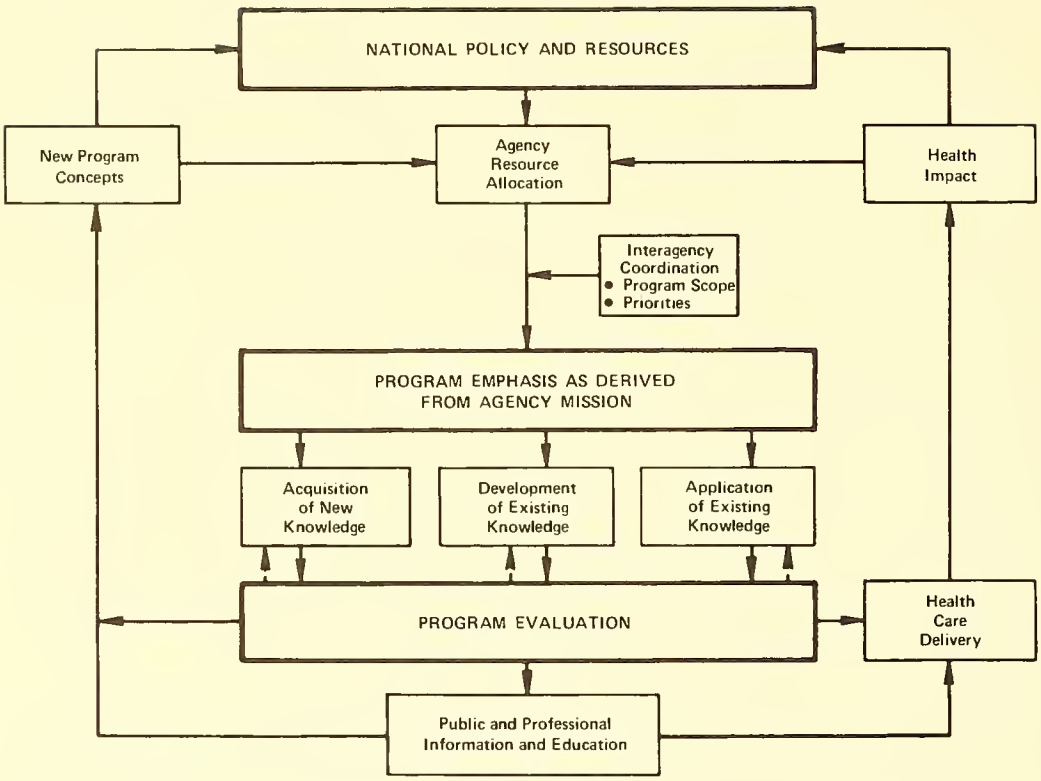


Figure 1. Coordination and Implementation of the National Program

From a central position, the Institute can review current knowledge and activities in each program area addressed by the National Program and thereby assure balance among the program areas. Most importantly, the Institute as coordinator of the National Program will be able to stimulate the development and dissemination of information to the public and the medical professions in a responsible and timely manner.

Key collaborative efforts in areas related to the problems addressed in the National Program are conducted through a variety of mechanisms. Some of these national efforts are summarized below. Highlights of relevant cooperative agreements between the NHLI and other countries are also presented, insofar as these represent extensions of a National Program which addresses transnational disease problems.

NATIONAL COLLABORATION

A key formal mechanism for coordinating national efforts related to the National Program is the Interagency Technical Committee on Heart, Blood Vessel, Lung, and Blood Diseases and Blood Resources (IATC). The IATC was established by the Secretary of the Department of Health, Education, and Welfare in November 1972, in accordance with the National Heart, Blood Vessel, Lung, and Blood Act of 1972. This Committee, chaired by the Director of the National Heart and Lung Institute, is responsible for coordinating Federal agency activities related to heart, blood vessel, lung, and blood diseases and blood resources to assure their adequacy and technical soundness. The Committee provides a forum for communication and exchange of necessary information.

The Committee is comprised of representatives from the following components of the Department of Health, Education, and Welfare:

- Alcohol, Drug Abuse, and Mental Health Administration
- Center for Disease Control
- Food and Drug Administration
- Health Resources Administration
- Health Services Administration
- National Institutes of Health
- Social and Rehabilitation Service
- Social Security Administration.

Also on the Committee are representatives from other Federal departments and agencies as follows:

- Department of Agriculture
- Department of Defense
- Department of Transportation
- Atomic Energy Commission
- Environmental Protection Agency
- National Aeronautics and Space Administration
- National Science Foundation
- Veterans Administration.

During the initial planning effort, the Committee provided input to the National Program by advising on goals, opportunities, and needs. It also assisted the Institute in compiling an inventory of ongoing programs related to the National Program. This inventory, published as Volume V of the National Heart, Blood Vessel, Lung, and Blood Program, identified, within only the agencies represented on the Committee, approximately 3,500 research areas related to the National Program. These programs represented more than $130 million in Federal outlays above the NHLI's budget for these related programs.

Presently, the Committee is updating the information contained in Volume V (by provision of FY 73 data) and reviewing the status of past and present interagency coordination and the prospects for broadened agency participation in the National Program.

In addition to the information displayed in Volume V last year, there are other Federal organizations which are not represented on the IATC, but which conduct or sponsor related research and/or prevention, control, and education activities in heart, blood vessel, lung, and blood diseases and resources. Furthermore, 24 non-Federal voluntary organizations with related programs were identified in Volume I last year. The NHLI already collaborates with many of the Federal and non-Federal organizations and plans even greater collaboration in the future among all the sectors of our society concerned with these disease problems. Discussed below, for each major disease category, are some key ongoing collaborative efforts in which the NHLI participates.

HEART AND BLOOD VESSEL DISEASES

Many major collaborative and cooperative efforts already exist with Federal and non-Federal organizations, professional societies, and the private sector. Examples given below include Nutrition; Hypertension; High Blood Pressure Education Program: Devices; Emergency Medical Services; Pacemakers and the Artificial Heart; Rehabilitation; Cardiac Reconditioning; and Manpower Development.

- **Nutrition.** The NHLI is collaborating directly with the U.S. Department of Agriculture (USDA) and the Food and Drug Administration (FDA) in defining data gaps and updating and publishing a new authoritative nutrient composition source book to supersede a previous edition outdated by the new processed and convenience foods. Completion of this effort will provide the basic data necessary to enumerate dietary constituents for research on the effect of diet on blood lipids and heart disease. Information received from the FDA on its new voluntary food labeling regulations and commercial food analyses made by the Grocery Manufacturers of America for the USDA's National Food Data Bank are now being channeled directly to the NHLI.

- **Hypertension.** The National High Blood Pressure Education Program has as its major goal the reduction of morbidity and mortality from high blood pressure and its sequelae. The NHLI has lead responsibility for coordinating this program which is an interagency, Federal/non-Federal cooperative effort. The Health Services Administration, Health Resources Administration, Food and Drug Administration, Veterans Administration, and Department of Defense have all designated representatives to the program. During the first year of the program, the Veterans Administration, Food and Drug Administration, Health Services and Mental Health Administration, and National Institutes of Health were represented on four Task Forces which made recommendations on data base, professional education, community education, and national resources and impact assessment. The Department of Defense was also represented on the Professional Education Task Force.

  Besides representation in the planning effort, several agencies took responsibility for implementing some of the Action items during the past year. The Health Services and Mental Health Administration sponsored the development of mass media educational materials; the Food and Drug Administration sponsored a workshop on professional education and is sponsoring a survey of physicians on high blood pressure; the NHLI sponsored a public attitude survey on high blood pressure and a national conference on high blood pressure education; and various other activities were sponsored jointly by several agencies.

  The program has a policy of cooperating with any organization which wants to produce educational materials, and will supply technical advice and allow the use of the logo, provided the material does not endorse any particular product(s), is not for sale, and is factually correct. The response from the private sector has been gratifying. Educational materials for the public and the medical professionals have been produced with a consistent message. Professional and voluntary organizations such as the American Medical Association, American Heart Association, National Medical Association, American Public Health Association, and American Red Cross have endorsed the program. The program also cooperates closely with a newly formed group, the Citizens for the Treatment of High Blood Pressure.

- **High Blood Pressure Education Program: Devices.** Hypertension is recognized as a significant community health problem. Mass screening programs for the detection of hypertension are currently being initiated. In view of the needs of these programs, several community groups have asked for guidance in choosing an automated device for measuring blood pressure. For this reason the NHLI, as the lead agency for the National High Blood Pressure Education Program, has initiated a review of the status of automated

blood pressure measuring devices with a task force to assess these devices. Representatives from the Food and Drug Administration and the Veterans Administration are among those helping in the evaluation. The NHLI will also work with the American Heart Association through the Committee on Criteria and Methods of the Council on Epidemiology. A proposal for evaluating automated blood pressure measuring devices, as well as criteria for a suitable device, has been developed by the American Heart Association committees. This work will be of great help to the NHLI Task Force as it attempts to look at all the devices currently available and to assess them in terms of suitability criteria.

- **Emergency Medical Services.** In the fall of 1972, the Secretary of Health, Education, and Welfare established an Interdepartmental Committee on Emergency Medical Services with the then Health Services and Mental Health Administration assuming the lead role. The Associate Director for Cardiology, Division of Heart and Vascular Diseases, NHLI, was appointed the NIH representative. The NHLI has collaborated with the Emergency Medical Services Branch of the Health Resources Administration on topics of mutual interest and importance, including co-sponsorship of the Second National Conference on Emergency Health Services and of the meeting on Cardiopulmonary Resuscitation sponsored by the American Red Cross and the National Science Foundation. Within the context of the National Program, the NHLI will be responsible for the elucidation of the pathophysiology of heart disease in its earliest emergency phases and for the development of methods of care suitable for incorporation into emergency medical care systems.

- **Pacemakers and the Artificial Heart.** Collaborative efforts between the Atomic Energy Commission (AEC) and the NHLI date back to 1965, when the AEC initiated a program for a radioisotope-powered cardiac pacemaker with the consultative advice of the NHLI. The reliability of these devices, tested in animals by the NHLI, has been demonstrated at a level sufficient to permit clinical implantation in approximately 50 patients throughout the nation, including several within the clinics of NHLI.

  From the inception of the Artificial Heart Program in the early 1960's, the NHLI and the AEC have collaborated in determining feasibility and exchanging technological information. Initial feasibility studies were jointly funded and assessed. There has been a renewed and markedly strengthened effort at regular scientific interchange and semi-annual formal meetings between the NHLI and the AEC with respect to artificial

heart development. Through these contacts and the interchange of documents, the NHLI has made available to the AEC recent progress and research information on its programs. The AEC, in turn, is making available to the NHLI a 33-watt encapsulated plutonium source for conducting important studies.

- **Rehabilitation.** Coronary artery disease is responsible for chronic disease in several million Americans, including 2.5 million Americans less than 65 years old. The NHLI has convened a task force to study the present state of our knowledge as it relates to cardiac rehabilitation. This task force will assess the state of the art, the medical and social import of cardiac rehabilitation, and present techniques and their scientific bases. Recommendations will be developed for clinical implementation of what is known and practical, and for initiating effective research where necessary. Representatives from community and governmental agencies (including the American Heart Association, the Council of State Administrators of Vocational Rehabilitation, the Rehabilitation Services Administration, the Social and Rehabilitation Service) are working closely with the NHLI to develop and implement an overall plan on cardiac rehabilitation.

- **Cardiac Reconditioning.** The NHLI is using the results of and collaborating in research and implementation of activities related to cardiac functions with the National Aeronautics and Space Administration (NASA). In collaboration with NASA, NHLI is evaluating the effects of weightlessness on cardiovascular function. Although previous NASA studies of astronauts returning from space missions indicate that profound, but apparently reversible, changes occur in various bodily functions, the effect of prolonged weightlessness on cardiac function is unknown. Several observations which suggest that the heart may be affected adversely include: (1) necropsy studies on the three Soviet cosmonauts who died during re-entry suggested that the heart might have undergone severe degenerative changes during their space voyage; (2) heart size as determined from frontal X-rays on American astronauts have demonstrated the heart to be smaller immediately post-flight as compared to pre-flight; (3) postural hypotension is an invariable early post-flight finding; and (4) NASA scientists have determined that, when compared to control pre-flight studies, cardiac output during exercise often is markedly reduced shortly after splashdown.

To follow up on these observations, the NHLI is collaborating with the biomedical staff of NASA to systematically evaluate

the effects of prolonged weightlessness on cardiovascular function. Pre-flight studies on the astronauts and back-up crew of the Skylab III mission have been completed. Post-flight repeat studies are planned.

Over the past three years, the NHLI has been refining the technology of echocardiography and applying this technology to the evaluation of patients with all types of cardiac disease. Echocardiography is a diagnostic procedure that utilizes ultrasound to visualize noninvasively the internal structures of the heart. This technique will be used to help determine whether prolonged weightlessness leads to myocardial atrophy, whether myocardial function is impaired, or whether all of the observations to date can be explained by a decrease in circulating blood volume. The adequacy of baroreceptor-mediated reflexes will also be investigated. Finally, by serial measurements over the course of weeks or months, these collaborative studies will assess the reversibility of any abnormalities that develop and the time it takes for return to normal function. These studies could result in generally applicable information concerning, for example, reversibility of certain types of cardiac abnormalities.

- **Manpower Development.** As described in the chapter on Manpower Development, the NHLI has collaborated with a number of professional and private organizations to conduct an in-depth assessment of current manpower status and future needs in a variety of disciplines related to the National Program in heart and blood vessel diseases. Examples of these organizations are the American College of Cardiology, American Association for Thoracic Surgery, and the American Heart Association.

LUNG DISEASES

Two major cooperative programs reinforce the Institute's Actions for prevention, control, and education activities in smoking and black lung. Other cooperative programs relate to structure and function of the lung and to manpower development. These are described below:

- **Smoking.** Cooperative efforts to reduce smoking and its harmful effects on health are being conducted with the National Cancer Institute (NCI), National Clearinghouse for Smoking and Health, and the Veterans Administration. The goals of these efforts are to develop a less hazardous cigarette and to study smoking behavior and its modification, and to

utilize these findings in developing an intervention program in the general population. Two specific programs funded jointly by NCI and NHLI to achieve these goals are:

- Experiments to Determine Effects of High and Low Nicotine Cigarettes. The purpose of these experiments being conducted by the Veterans Administration is to determine whether nicotine is involved in the harmful effects produced by inhalation of cigarette smoke over many months.

- Comprehensive Smoking Withdrawal Program. This program, also funded by the National Clearinghouse for Smoking and Health, is designed to conduct a research and demonstration project aimed at developing a community-based comprehensive control program which would provide services on an individual referral basis as well as to industry, civic, and community organizations.

- **Pneumoconioses (Black Lung).** Because coal miners are at high risk of developing respiratory diseases from exposure to airborne dusts, a joint committee, the Working Party on Respiratory Diseases Among Coal Miners, has been established, at the request of the Governor of Pennsylvania, to define the types of efforts most urgently required to prevent or treat work-related respiratory diseases. This committee has members from Federal (National Institute for Occupational Safety and Health, National Institute of Environmental Health Sciences, U.S. Bureau of Mines, and NHLI), State (Commonwealth of Pennsylvania), non-profit (New York Academy of Sciences, American Lung Association), industry (such as U.S. Steel and others), and university organizations.

  The Working Party has four subcommittees: (1) Subcommittee on Clinical Problems, with the charge to develop an optimal clinical management program, develop simple tests for diagnosis and effectiveness of therapy, and develop specific graduate educational and physician education programs; (2) Subcommittee on Research Perspectives in Epidemiology and Small Airway Disease, with the charge to study small airway disease in coal workers and investigate the epidemiology of coal worker's respiratory disease; (3) Subcommittee on Research Perspectives Concerning Biologically Important Particles in Coal Worker's Pneumoconiosis, with the charge to study the ultramicroscopic particles in relation to the problem and investigate the inactivation of dust in the lungs; (4) Subcommittee on Prevention and Treatment of Coal Worker's Respiratory Disease, with the charge to investigate the pathogenesis of Progressive Massive Fibrosis and investigate the cellular biology approach to the problem. The Working Party has scheduled a series of meetings to identify and delineate areas for further development and action.

- **Pressure and Underwater Biomedical Research.** The NHLI is participating in a National Cooperative Program of Pressure and Underwater Biomedical Research and Operation Development with the Department of the Navy and the National Oceanic and Atmospheric Administration. The objective of this program is to identify critical biomedical problems related to respiration and underwater pressure and to recommend steps for their solution. The focus of the program is on determining alterations in the various body systems when responding to increasing physical and physiological stresses over long periods of time. As one system is progressively stressed, e.g., the respiratory system, the effects are initially compensated by alterations in other systems, e.g., the circulatory or renal systems. As the limit of compensatory processes are reached, failure in functions begins and may progress to complete failure if the stress continues. The respiratory system is the prime target of this research which promises to provide important insights into the structure and function of the lung.

- **Manpower Development.** The NHLI has collaborated with the American Thoracic Society and the American College of Physicians in surveying the national needs for manpower in pulmonary diseases. Conclusions drawn from these surveys are presented in the chapter on Manpower Development. The Institute is also coordinating its activities in this area with the American Lung Association and other voluntary organizations interested in the implementation of the National Program.

BLOOD DISEASES AND BLOOD RESOURCES

The National Program in blood diseases and blood resources sets forth a number of key research and prevention Actions for ameliorating the effects of sickle cell disease, Cooley's anemia, hemophilia, and hepatitis, and for improving the management of our nation's blood resources so vital to the treatment of disease. Important cooperative efforts relevant to the National Program have been initiated. Examples of these efforts related to the above Actions are described below.

- **Sickle Cell Disease.** Cooperative efforts between NHLI, the Health Services Administration (HSA), and the Center for Disease Control (CDC) are ongoing in this area. Demonstration, screening, and education programs have been developed by NHLI and HSA. Cooperative efforts have been developed with CDC to carry out (1) workshops in hemoglobinopathy detection, (2) a proficiency testing program for DHEW-funded projects, and (3) the establishment of reference laboratories for abnormal hemoglobins.

- **Cooley's Anemia.** NHLI cooperation with other NIH components, with private organizations involved with Cooley's anemia, and with the scientific community has led to agreement regarding priorities for research in this area.

- **Hemophilia.** The NHLI maintains a cooperative working relationship with the National Hemophilia Foundation. Collaborative activities include program planning, information exchange, and research. The Foundation had significant input into the development of the National Program, and discussions are now in progress to assure that the programs of the NHLI and the Foundation are complementary and mutually supportive of each other. With the assistance of the Foundation, the NHLI recently published a pilot study of hemophilia treatment in the United States.

- **Hepatitis.** A Hepatitis Liaison Committee composed of representatives from all government organizations funding hepatitis research has been established to coordinate information exchange and to advise all research organizations on program needs and potentials. This Committee has supported a workshop on the future of epidemiologic studies in hepatitis. A Hepatitis Policy Liaison Committee (Bureau of Biologics, NHLI, and National Institute of Allergy and Infectious Diseases) coordinates extramural hepatitis research activities funded by the component agencies.

- **Blood Resources.** The NHLI maintains continuing liaison with the three major blood suppliers in the U.S.: the American National Red Cross, the American Association of Blood Banks, and the Council of Community Blood Centers. These organizations have been charged by the Secretary of Health, Education, and Welfare to develop implementation plans for a National Blood Policy. The NHLI works closely with the Food and Drug Administration in regulatory areas relating to safety and efficacy of blood products and handling.

- **Manpower Development.** The NHLI, in cooperation with the National Institute of Arthritis, Metabolism, and Digestive Diseases (NIAMDD) and the American Society of Hematology (ASH), has drafted a proposal for manpower development in research hematology in the United States. This proposal was drafted with input from a broad segment of the academic hematologic community.

INTERNATIONAL COLLABORATION

The disease problems addressed by the National Program are transnational. They are major problems encountered by all peoples throughout the world. Implementation of the National Program provides a real opportunity for exchange of information between countries on problems of heart, blood vessel, lung, and blood diseases and blood resources. The planned research and prevention, control, and education programs in the United States can be greatly enhanced through cooperation with other countries which are trying to solve these problems within their own borders. Cooperation with other countries enhances and strengthens the capability of the Institute for effective national collaboration for the benefit of our citizens. During FY 73, the Institute supported 34 foreign projects and fellowships in areas related to the National Program. The recently initiated US-USSR Health Exchange Program is a highly structured, collaborative international program related to the goals of the National Program.

In 1956, the National Heart Institute participated for the first time in the US-USSR Scientific Exchange Missions. Since that time, American scientists have visited research and treatment centers in the Soviet Union and Soviet scientists have visited heart research centers in the United States. An expansion of cooperation, including mutual planning and execution of joint research activities, between the two countries in the field of health and medical science was agreed upon in February 1972. A five-year agreement was signed three months later. The cardiovascular area was one of the first three areas recommended for such expanded cooperation. The Director of the National Heart and Lung Institute is the overall U.S. coordinator for the cardiovascular studies. Key activities related to the National Program which are being implemented under this agreement are briefly described below:

- **Pathogenesis of Arteriosclerosis.** Arteriosclerosis is the most common type of cardiovascular disease and the chief cause of death in both the U.S. and the U.S.S.R. A joint clinical study has been undertaken to determine the prevalence in both countries of hyperlipidemias and ischemic heart disease, and the effect of modifying blood lipids by diet or drugs on the risk of developing these diseases. This is the first study of its kind in the world. It involves large numbers of well-characterized subjects in two countries, comprehensively studied according to identical techniques based on carefully worked out research protocols, and analyzed by highly standardized techniques.

- **Management of Ischemic Heart Disease.** Ischemic heart disease is the most common clinical complication of arteriosclerosis and the most common complication leading to death. The U.S., through the NHLI, and the U.S.S.R. are conducting a comparative study of different approaches for medical and surgical treatment of ischemic heart disease. This project, also the first of its kind, will evaluate and compare chronic angina and heart attack disability treatment methods that have been developed in each country.

- **Myocardial Metabolism.** This topic involves the study of the activities and functions of both the healthy and the diseased heart. Thus, it is relevant to the study of all types of heart disease. During the past year, American and Russian scientists have exchanged information on methods to limit the extent of heart muscle damaged by heart attack. These findings will be published jointly.

- **Congenital Heart Disease.** Congenital heart disease affects an estimated 25,000 children born in the U.S. each year and a corresponding number born in the U.S.S.R. each year. The objectives of this collaborative study are to develop diagnostic techniques and methods of post-operative care, to study the mechanisms of development of pulmonary hypertension, to search for new ways of reducing mortality from the surgical treatment of tetralogy of Fallot, and to study diagnostic techniques and surgical treatment of complex heart defects.

- **Sudden Death.** This problem is a new initiative for collaboration in the cardiovascular area. Exchange of information, exchange of health professionals, and meetings between Russian and American specialists are in progress to develop detailed plans for scientific cooperation.

- **Blood Transfusion, Blood Components, and Prevention of Hepatitis, with Particular Reference to Cardiovascular Surgery.** This problem is also a new initiative for collaboration in the cardiovascular area. Exchange of information, exchange of health professionals, and meetings between Russian and American specialists are being held to develop plans for scientific cooperation.

- **Technological Development.** A joint program in mechanical circulatory assistance is under development.

The actions and schedules for these programs are updated annually by the joint US-USSR committee in light of recent progress and future challenges.

V. MANPOWER DEVELOPMENT

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The development and maintenance of highly skilled manpower at all levels are of great importance in the planning and implementation of our national effort against heart, blood vessel, lung, and blood diseases. This is true both from the standpoint of the professionals participating in the Program and the public paying for and benefiting from the Program. Recruitment, selection, training, development, and support of talented young scientists are critical to the continued success of the National Program. The search for new solutions to these disease problems will make new demands on the nation for adequate numbers of well-trained personnel. The scientists, physicians, and allied health professionals engaged in this effort must be familiar with many new and complex technologies and must be educated to draw experience from old technologies. They must be ready and willing to engage in intellectual pursuits which will help in finding new answers.

The National Heart and Lung Advisory Council, in both its initial Report of April 1973 and in its first Annual Report of December 1973, places great emphasis on the need to develop skilled manpower. This is needed not only to replace losses from the present pool through attrition, but also to search for innovative approaches to the disease problems addressed by the National Program. The NHLI Summary of May 1973 recognized the importance of manpower development. However, the Institute's position was that any specific recommendations should be keyed to documented needs in specific areas. Therefore, recommendations were deferred at that time, pending results of a major review of manpower needs in those disciplines that affect implementation of the National Program.

In considering the manpower needs for the expanded national effort, three factors must be given careful consideration:

- Manpower development, research, and health care are three segments of an interrelated continuum, and manpower development cannot be considered separately from research or health care any more than research *per se* can be considered separately from health care.

- Manpower development needs will continue to grow as the store of knowledge (now doubling every ten years) grows through research, as the population grows, and as the public demands new and increasingly sophisticated approaches to health care.

- There is an increasing demand for public accountability of all health professionals, since the public is the source of funds as well as the ultimate beneficiary of manpower development, health research, and health care. Thus, the public must be given confidence that every effort is being made to assure high quality of professional performance throughout the program--in planning, research, prevention, education, control, evaluation, and coordination.

Data so far collected indicate the positive need for a vigorous manpower development program for the advancement of future research and investigation. This is based on analysis of a number of surveys and assessments by Institute staff, members of the National Heart and Lung Advisory Council, voluntary agencies, and professional organizations. The estimates below are conservative and were derived by assessing:

- The minimum number of research investigators needed for the maintenance of selected, vital research activities

- The minimum number of trained investigators currently needed to fill documented and budgeted faculty vacancies directly related to the mission of the NHLI

- The particular talents, disciplines, or areas that need additional manpower for implementing a vigorous National Program.

HEART AND BLOOD VESSEL DISEASES

There are approximately 11,000 active cardiologists in this country, with a considerable variation in geographic distribution. In a recent survey, fully 5 percent of the active cardiology training programs had no full-time faculty member. Furthermore, almost 30 percent of the training programs had an average of two staff positions that were budgeted but unfilled, representing a national total of 150 to 180 positions in this category. A separate survey revealed that only 94 medical centers in the United States had certified pediatric cardiologists on their staffs, representing a shortage of approximately 100 pediatric cardiologists in this country. Taking annual losses into account, it is estimated that 350 to 400 individuals would have to be added to the research manpower pool each year

merely to maintain the present status of heart and blood vessel research efforts. Thus, the Institute estimates that, at a minimum, approximately 600 individuals should be enrolled in fellowship or trainee programs related to heart and blood vessel diseases in order to maintain the present level and to implement the Action items in the National Program.

- The NHLI proposes to place special emphasis on training in those areas in which research skills are currently in short supply, namely: pediatric cardiology, behavioral and motivational disciplines, bioengineering (with a particular view to improving noninvasive diagnostic instrumentation), genetics (as related to a variety of disease states such as hypertension and abnormal lipid metabolism), pediatric nutrition and metabolism (as related to lipid metabolism), microcirculation (including aspects of blood flow and tissue metabolism), immunochemistry, and epidemiology and biostatistics.

LUNG DISEASES

A recent survey of professional manpower revealed that 130 currently funded but unfilled vacancies exist on medical school faculties in lung diseases and at least 20 additional vacancies exist at research institutes. It is estimated that, within the next two to three years, approximately 550 well-trained individuals will be required for the staffs of medical schools and research institutions engaged in lung disease activities.

Research in the pulmonary disease area has now developed special and almost unique requirements. Increasingly, it has become possible to study lung diseases by investigation of underlying mechanisms, and physicians and scientists must now draw upon fundamental disciplines that are comparatively new to the lung field, such as biochemistry, cell biology, immunology, and bioengineering.

Because of the great need for interdisciplinary research and training in the lung diseases area, the Institute plans to give high priority to such programs. To date, basic scientists have not been conversant with the problems of lung diseases, and pulmonary clinicians have been generally uninformed about the basic studies that might contribute to their research.

- The NHLI believes that for these special interdisciplinary research training programs, where new and basic contributions can be made, between 150 and 200 research fellows should be supported in the immediate future.

BLOOD DISEASES AND BLOOD RESOURCES

Two separate studies of staff positions in academic hematology, focusing upon institutions with academic programs in blood diseases and blood resources, revealed that about 10 percent of the positions in academic hematology are unfilled. Research areas with the largest number of unfilled positions included hemoglobinopathies, coagulation, immunohematology, and blood banking--all areas of major concern in the National Program.

The development of manpower for blood banking is one of special urgency in the United States. Not only is there a lack of adequately trained manpower in blood banking, but there are also insufficient training faculties and resources. These limitations have prevented the effective application of newer techniques and knowledge in this area of health care vital for the American people.

- The Institute estimates that approximately 200 research fellows should be trained now in the blood research areas addressed by the National Program. The efforts in this regard will be coordinated with other Institutes of the NIH involved in hematology manpower development. The areas of special need include: blood banking, platelet function and abnormalities, thrombosis in the microcirculation, thromboembolism, abnormal hemoglobins including sickle cell disease, red blood cell membranes and enzyme systems, and the biology of transplantation of tissues and organs.

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Since the training required in all of the above areas is highly specialized, it will take several years or more before the individuals enrolled in the programs will be ready to contribute fully to the activities of the National Program. Prompt initiation of these manpower development programs is of major importance. Otherwise, implementation and progress of the National Program will be impeded.

VI. IMPLEMENTATION OF OTHER PROVISIONS OF THE ACT

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The passage of the National Heart, Blood Vessel, Lung, and Blood Act of 1972 significantly expanded the Institute's mandate and responsibilities. To implement the new and increased activities authorized by the Act in an efficient and timely manner, the National Heart and Lung Institute has made significant changes in its organizational structure, program management, and ways of communicating and collaborating with the public and the professional community in the National Program. Five areas of special importance to the successful implementation of the National Program are discussed in this chapter:

- National Research and Demonstration Centers
- Construction
- Mechanisms of Support
- Administrative Changes
- Program Review and Evaluation.

NATIONAL RESEARCH AND DEMONSTRATION CENTERS

P.L. 92-423 states that the Director of the Institute may provide for the development of National Research and Demonstration Centers: up to 15 Centers for problems related to heart, blood vessel, and blood diseases, and up to 15 Centers for problems related to chronic lung diseases. The purpose of the Centers' program is to facilitate and expedite the translation of research results to clinical practice in local communities across the nation. The Legislative Act specifies that the programs of such Centers would encompass basic and clinical research into, training in, and demonstration of, advanced diagnostic, prevention, and treatment methods for the respective diseases. In the initial National Plan, the NHLI proposed to

establish approximately five Centers in FY 74 and an additional five in FY 75, at an initial level of about $1 million per Center in the first year, rising incrementally to about $3 million per Center in the third year. After further study and on advice of the National Heart and Lung Advisory Council, we now estimate the initial operational cost per Center at approximately $3 million per year.

A Program Announcement and Guidelines, developed with advice from the National Heart and Lung Advisory Council, were released in August 1973. A National Research and Demonstration Center is defined as a national resource attached to a major medical complex and dedicated to working in close collaboration with the Institute to further the goals of the National Program. A Center preferably should focus on one major area--heart and blood vessel diseases, lung diseases, blood diseases, or blood resources. However, a combination of areas would be acceptable if shown to be more effective in meeting the goals of the National Program. The guidelines require that each Center must include programs in fundamental research, clinical research and clinical application, an environment conducive to the training of young scientists, and an information and education program.

A meeting of potential applicants was held at the National Institutes of Health early in October 1973. More than 300 representatives from interested institutions attended and NHLI staff answered questions and clarified specific aspects of the program. Approximately 75 letters-of-intent to apply have been received: 31 in heart and blood vessel diseases, 21 in lung diseases, 15 in blood, 5 combining heart and lung diseases, and a few not classified. Formal applications are due early in 1974.

Proposals for the Centers will be reviewed in the spring of 1974 by panels of expert consultants and by the National Heart and Lung Advisory Council. The ability of the Institute to make any awards for National Research and Demonstration Centers is contingent upon the availability of appropriated funds. The Institute plans to activate the program early in FY 75. Additional Centers may be activated in the future as the effectiveness of the first group is determined, and as experience is gained in the planning, monitoring, and execution of these multidisciplinary programs.

CONSTRUCTION

The National Heart and Lung Advisory Council, in its first Annual Report, reiterates the need for funds for construction of facilities to develop the required capabilities for full implementation of the National Program. This is particularly true for the National Research and Demonstration Centers. Funds for construction are not included in the NHLI fiscal allocation plan for FY 74. Therefore, initial Centers must provide for all facilities and resources necessary to initiate the program. However, the Centers will serve as national resources for expediting the transfer of research results to national clinical practices,

and additional facilities will be needed as each Center becomes fully operational. In the initial NHLI Plan, the Institute estimated the net space requirements of each Center as approximately 80,000 to 100,000 square feet, and further estimated that approximately 60 percent of this space might have to be newly constructed. Projections are included in the budget for 450,000 square feet in FY 76, 225,000 square feet in FY 77, and 225,000 square feet in FY 78 to provide for new construction for the Centers, and an additional 60,000 square feet for other specialized research facilities for the National Program. These estimates are based on the establishment of 15 Centers, each with a space requirement of approximately 100,000 square feet, and assuming that the government will pay for the 60 percent which is newly constructed.

A long lead time for planning and executing construction projects is not unusual. Therefore, the Institute again recommends that funds appropriated for this purpose remain available through the year subsequent to the one in which they are appropriated, with the proviso that they be used for construction only.

MECHANISMS OF SUPPORT

Implementation of the programs of research and prevention, control, and education that collectively make up the National Program involves the participation of a broad range of biomedical professionals. Support is provided through a variety of mechanisms. As outlined in the initial NHLI plan, these mechanisms range from the traditional research project grant, for the independent investigator who wishes to contribute to the National Program by carrying out relevant research according to a plan initiated by himself, to highly structured research contracts, for investigators who wish to participate in programs which are addressed to sharply targeted goals and solicited and monitored by the Institute. Between these two mechanisms are larger multidisciplinary programs, such as the current Specialized Centers of Research and the proposed National Research and Demonstration Centers. These multidisciplinary efforts, although grant-supported, combine a degree of investigator independence with mission-orientation and a close working relationship with the Institute in order to integrate the efforts of one Center with the activities of other Centers and with those of the Institute.

The Institute will continue to use the fiscal mechanisms most appropriate to given activities. Independent research must continue and be fostered as a major source of new and fresh ideas for scientific advance. At the same time the Institute has a responsibility to society to facilitate the transfer of these scientific advances to the American health care system. Table 3 shows the allocation of funds between grants and contracts in FY 73. We would expect that the distribution of funds among these mechanisms will remain substantially unchanged in FY 74. The Institute does not plan any significant change in this ratio of distribution in the near future. The Intramural Research noted in the table is the in-house program of basic and clinical research carried out at the National Institutes of Health.

Table 3. NHLI Resource Allocation by Major Activity

Activity	Percent of Funds FY 1973
Research Grants	54.8
Training Grants and Fellowships	8.9
Research Contracts	24.0
Intramural Research	7.6
Research Management and Program Services	4.7
TOTAL	100.0%

ADMINISTRATIVE CHANGES

During the past year, the National Heart and Lung Institute has made four major administrative changes:

- Reorganization of the Institute
- Appointment of an Assistant Director for Health Information Programs
- Creation of an Office of Prevention, Control, and Education
- Expansion of the National Heart and Lung Advisory Council.

The Institute's activities during the past three years have broadened to include additional programs in lung and blood diseases, demonstration and control responsibilities, and additional program-oriented efforts, such as National Research and Demonstration Centers. In line with these program changes, the NHLI examined its basic organization and concluded that the Institute had developed to a stage where the primary organization should be mainly by subject matter rather than by mechanism of support. Consequently, the Institute has been reorganized into five divisions: Division of Heart and Vascular Diseases, Division of Lung Diseases, Division of Blood Diseases and Resources, Division of Intramural Research, and Division of Extramural Affairs.

The National Heart, Blood Vessel, Lung, and Blood Act authorizes the Director of the Institute to appoint an Assistant Director for Health Information Programs responsible for disseminating health information with particular emphasis on risk factors and preventive measures. The Act also authorizes the Director to establish Prevention, Control, and Education Programs for Heart, Blood Vessel, Lung, and Blood Diseases. Both provisions have been implemented. The Assistant Director for Health Information Programs heads the newly activated Office of Prevention, Control, and Education which is responsible for the prevention and control programs outlined in Chapter III of this report. The first programs under its aegis are already operational and relate to hypertension and to sickle cell disease.

The Act considerably expands the National Heart and Lung Advisory Council, both in membership and in responsibilities. In addition to developing its own Annual Report on the National Program, the Council plays an active role in development of the Institute's long-range program plans. The Act authorizes appointment of an Executive Secretary of the Council to assist the membership as needed. This position has been filled by a member of the professional staff of the Institute.

PROGRAM REVIEW AND EVALUATION

Approximately 300 biomedical specialists were involved in developing the National Program in heart, blood vessel, lung, and blood diseases and blood resources less than a year ago. Since that time, the activities of the National Program have been extensively reviewed and evaluated. Program goals, progress, challenges, actions, and schedules have been examined in terms of their relative importance to the overall program. As a result of this review process, a revised program structure was developed and changes were made in program direction (as set forth in Chapter III). These revisions form the basis for this annual report and updated 5-year Plan. Review and evaluation continues at each level of the Institute's programs and will continue to form the basis for each Annual Report of the Director and each annual updating of the 5-year Plan.

Furthermore, in implementing the program strategy (outlined in Chapter I), the Institute will review and evaluate each program as activities move in an ordered sequence from research to testing to application. Programs will be reviewed both before and after application in health care delivery systems. The Institute is developing procedures for ensuring that these review processes are both appropriate and effective.

In addition, a number of specific evaluation efforts are underway or planned. These studies involve the effectiveness of Specialized Centers of Research programs, the effectiveness of contract programs in lung diseases and the Pulmonary Academic Award Program, rehabilitation of the patient after myocardial infarction, management of the national blood resource, assessment of the status of left heart assist devices, and the role of cultural factors in the development of heart and blood vessel diseases.

An Artificial Heart Assessment Panel was convened to assess the economic, ethical, legal, medical, psychiatric, and social implications of clinical application of a totally implantable artificial heart. The recommendations of this Panel have been submitted to the Institute and will be considered in future program developments.

Several studies of manpower availability have been supported in order to determine the manpower needs in various areas related to the National Program. These studies are discussed in Chapter V in this report. Training opportunities and manpower needs will be continually reviewed by the Institute since these factors will play a vital role in implementing the 5-Year National Plan.

VII. RESOURCE ALLOCATION PLAN

VII. RESOURCE ALLOCATION PLAN

The problems of heart, blood vessel, lung, and blood diseases represent both an indictment and an opportunity for action. As stated in Chapter I, "The United States, despite its high state of technology, lags behind many other Western nations in the health of its citizens. In fact, it ranks 24th in the world with respect to life expectancy for men. The high mortality from heart and blood vessel diseases is the major contributing factor to this shortened life expectancy." The National Heart, Blood Vessel, Lung, and Blood Program is an effort to correct these problems. It will require revision of national priorities and redistribution of resources to better serve the health needs of the American people.

In developing this report, the Institute has taken a hard look at ways in which the quality and comprehensiveness of the National Program can be improved. It has reexamined the priorities within each program area, developed plans to shift resources to more productive use, and revised its planned course of action over the next five years accordingly. Specifically, the NHLI has reviewed:

- The needs and opportunities for research, prevention, control, and education in heart, blood vessel, lung, and blood diseases and blood resources. (See Chapter III.)
- The real challenge of coordinating national efforts in these areas. (See Chapter IV.)
- Related manpower development requirements. (See Chapter V.)
- Facilities and mechanisms of support needed for implementation of the National Program. (See Chapter VI.)

This program review and evaluation has focused on national priorities and health needs of the American people. Program requirements have been developed within this framework by key personnel in the National Heart and Lung Institute with the advice of the National Heart and Lung Advisory Council. Our priority actions are described in earlier chapters of this report, and the resources needed to fulfill these NHLI-supported actions are presented here. Contributions to the National Program by non-NHLI-supported activities are not included in these resource projections.

FISCAL SUMMARY AND PROJECTIONS

The resource projections discussed in this section are based on scientific and professional judgement as to the resources required to accomplish program objectives within the time frame indicated. However, it is recognized that the allocation of national resources to execute the program must be determined in relationship to other competing national needs at any given time.

Acting upon the results of its program review and evaluation, the Institute has revised and updated the fiscal projections presented in the initial National Heart, Blood Vessel, Lung, and Blood Program (Volume I) in May 1973. The major reasons for these revisions are:

- Program monitoring and evaluation of research programs has resulted in identification of both expanded and reduced opportunities and needs in some program action areas. (See section on Research in Chapter III.)

- As indicated in Chapter II recent research findings have opened potentially new vistas which require exploration of new initiatives.

- Research and prevention, control, and education pilot program results have suggested or proven the need for and capability of expanding our prevention, control, and education programs. (See section on Prevention, Control, and Education in Chapter III.)

- Recently completed studies have provided us with a clearer insight into both manpower and facilities requirements. (See Chapters V and VI.)

The projected resource estimates for FY 76 to FY 80 are shown in Table 4. This projection is provided so that the planning process will stay in phase with the overall departmental planning and budgeting cycle. The table, organized according to the program activity categories discussed earlier in this report, provides fiscal projections for:

- Extramural research programs in heart and blood vessel diseases, in lung diseases, and in blood diseases and blood resources. Research allocations are also shown for each subprogram within these major disease categories.

- Continued implementation of special NHLI programs authorized by Public Law 92-423: the National Research and Demonstration Centers; Prevention, Control, and Education Programs; and construction of facilities.

Table 4. Projected Resource Allocations* for the National Heart, Blood Vessel, Lung, and Blood Program
FY 76 - FY 80
(Dollars in Millions)

Program Activities	Fiscal Years				
	1976	1977	1978	1979	1980
Extramural Research Programs					
Heart and Blood Vessel Diseases					
Arteriosclerosis	$ 57.20	$ 58.40	$ 60.40	$ 62.40	$ 60.10
Hypertension	31.20	32.20	33.30	33.80	32.30
Cerebrovascular Disease	3.80	3.90	4.00	4.10	4.10
Coronary Heart Disease	42.50	43.50	46.10	47.30	44.80
Peripheral Vascular Diseases	4.10	4.20	4.30	4.40	4.40
Arrhythmias	16.50	17.20	19.00	19.20	18.20
Heart Failure and Shock	20.60	21.30	23.60	24.90	23.70
Congenital and Rheumatic Heart Diseases	9.60	9.90	10.40	10.60	10.60
Cardiomyopathy and Infections of the Heart	3.80	3.90	5.20	6.50	7.00
Circulatory Assistance	19.90	20.90	23.90	30.90	34.80
Subtotal Heart and Blood Vessel Diseases	209.20	215.40	230.20	244.10	240.00
Lung Diseases					
Structure and Function of the Lung	7.70	8.00	8.60	9.20	8.80
Pediatric Pulmonary Diseases	10.30	10.80	11.20	12.00	11.50
Emphysema and Chronic Bronchitis	8.40	8.90	9.80	10.30	10.60
Fibrotic and Immunologic Lung Diseases	8.50	9.00	9.10	10.50	10.90
Respiratory Failure	7.10	7.20	7.60	8.00	8.00
Pulmonary Vascular Diseases	2.20	2.30	2.50	2.30	2.00
Inhalation Diseases	2.20	2.60	3.00	2.50	2.00
Respiratory Assistance	.80	1.00	1.20	1.20	1.20
Subtotal Lung Diseases	47.20	49.80	53.00	56.00	55.00
Blood Diseases and Blood Resources					
Bleeding and Clotting Disorders	19.54	20.08	19.98	19.73	18.03
Sickle Cell Disease and Related Disorders of the Red Blood Cell	18.05	18.77	19.44	20.32	19.32
Blood Resources	14.81	14.95	17.18	19.65	18.65
Biomaterials	3.10	4.00	4.20	4.20	4.00
Subtotal Blood Diseases and Blood Resources	55.50	57.80	60.80	63.90	60.00
National Research and Demonstration Centers	25.25	48.50	55.20	56.70	58.70
Prevention, Control, and Education Programs	31.80	38.30	39.00	37.50	38.30
Construction	60.00	30.00	30.00	—	—
Manpower	20.80	20.80	21.90	22.70	22.70
Intramural Research Programs	25.00	26.00	26.00	26.00	27.00
Research Management and Program Services	21.66	25.16	23.67	24.69	24.43
TOTAL	$496.41	$511.76	$539.77	$531.59	$526.13

*This tabulation gives the primary thrust of activities, even though these activities generally involve more than one subprogram.

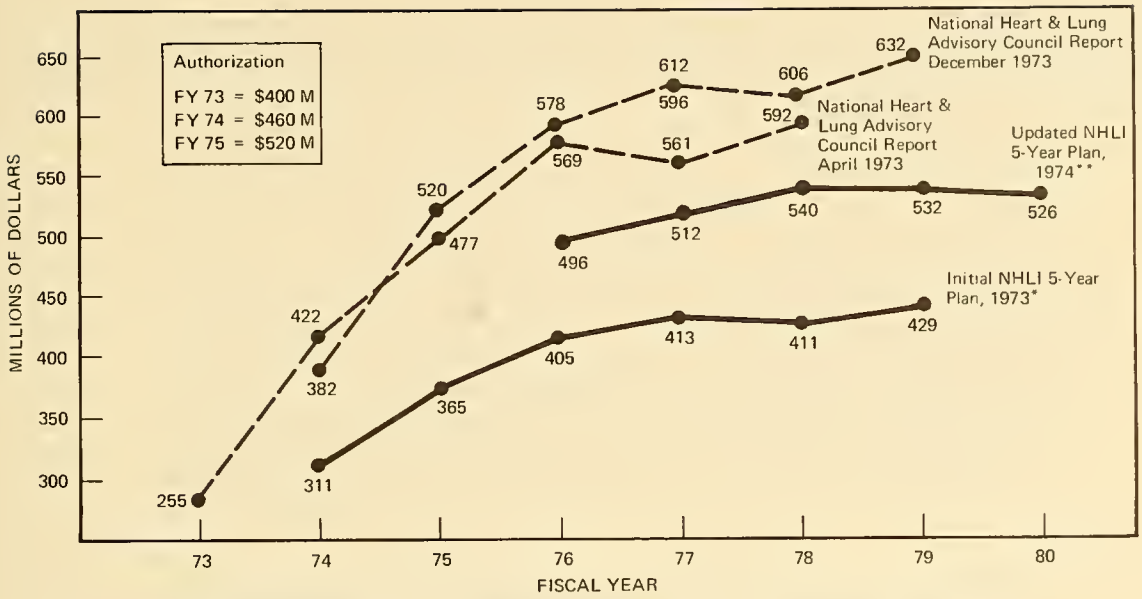
- NHLI's Intramural Research Programs, Manpower Development Programs, and Research Management and Program Services.

The resource allocations presented in Table 4 are consistent with the program activities projected and discussed in Chapters III, IV, V, and VI of this report. These allocations have been distributed in such a way as to build on past accomplishments and to anticipate future opportunities in specific program areas. In accordance with the legislation, at least 15 percent of the fiscal resources are projected for diseases of the lung and at least 15 percent toward the problems of blood diseases and resources.

It is important to point out that the projected resource allocations give the primary thrust of activities, even though these activities generally involve more than one subprogram, with some activities fundamental to many subprograms. Since subprograms cannot be made mutually exclusive, the allocation of a given project may be somewhat arbitrary. For example, a project involving the effects of arrhythmias in coronary heart disease upon heart failure would be categorized according to its primary thrust. A project on the movement of ions across cell membranes, which is fundamental to the causation and prevention of arrhythmias and heart failure and is applicable to all forms of heart disease and even to symptoms of cerebrovascular disease, would be allocated to multiple categories.

The fiscal requirements for the National Program total approximately $496 million in FY 76, an increase of $91 million over the previously recommended budget for FY 76. These requirements will increase incrementally to $540 million in FY 78; in FY 79, construction funds will not be required and the budget will decline to $532 million, followed by a subsequent reduction to $526 million in FY 80. The rationale for increased resource projections for certain programs in the 5-Year Plan was delineated in earlier sections of this report; however, we summarize in the following paragraphs the proposed program actions which require overall budget increases in the revised estimates projected here for FY 76 through FY 80. Figure 2 gives a comparison of the projected resource allocations for the Program in the 1973 and 1974 NHLI plans. It should be emphasized that resource projections have not been adjusted upward for inflationary increases since the 1973 plan was prepared. Similarly, the projections for fiscal years 1976 through 1980 are based on 1973 estimates of the costs of accomplishing program objectives.

There has been no change in the total projected estimates for the Extramural Research Programs in Heart and Blood Vessel Diseases, Lung Diseases, and Blood Diseases and Blood Resources. However, there have been internal readjustments of resources among subprograms in each of these program areas, reflecting revised priorities, new opportunities for action, and redistribution of resources to new programs. The total estimates for the NHLI's Intramural Research Program remain the same. Increased budget estimates have been projected over the next five years for the following extramural programs: Arteriosclerosis, Hypertension, Cerebrovascular Disease, Arrhythmias, Circulatory Assistance, Structure and Function of the Lung, and Pediatric Pulmonary Diseases.



*Does not include Research Management and Program Services, estimated at 4.87% of total estimated program costs.
**Includes Research Management and Program Services.

Figure 2. Comparison of Projected Resource Allocations for the National Heart, Blood Vessel, Lung, and Blood Program (FY 73 Through FY 80)

Although the fiscal projections for the remaining extramural subprograms represent decreases or no change since last year's projections, most of these programs will increase through FY 79, and decline in FY 80, in accordance with projected activities. Circulatory Assistance and Biomaterials, which were included under other subprograms in last year's Plan, have been given separate status in the revised Plan. The addition of three new program areas in lung diseases is balanced by a reduction in other areas of lung diseases. Two of these new areas are projected to increase slightly through FY 78 and decline thereafter through FY 80; the third, Respiratory Assistance, will grow gradually between FY 76 and FY 80. No major revisions have been made in the projected resource allocations for blood diseases and blood resources in FY 76, and gradual increments are currently projected in these areas between FY 76 and FY 79, closely following the projections in the initial Plan. The Intramural Research Program is, similarly, projected to gradually increase between FY 76 and FY 80 at the levels projected last year.

Five of the program activity areas listed in Table 4 account for the entire increase in the total revised resource allocation recommended for FY 76, as well as for the total budget increases projected from FY 76 through FY 80. These areas are: National Research and Demonstration Centers; Prevention, Control, and Education Programs; Construction; Manpower; and Research Management and Program Services. Among these five expanding areas, it is currently projected that construction funds will be required in fiscal years 1976, 1977, and 1978. Research Management and Program Services, which were not included in the May 1, 1973, estimates, account for about $22 million of the $91 million increase in the FY 76 projected estimates.

Within the overall fiscal limitations identified above, the major increases that have been projected in the revised fiscal allocations are required in order to support heightened program activity in each area. Key aspects of these activities are summarized as follows:

- **Arteriosclerosis.** Research has provided significant new knowledge about the causes and development of arteriosclerosis. Current research supports the feasibility of early diagnosis (including at birth); expanded programs are required to evaluate these research opportunities. The relationship of genetic factors to the development of arteriosclerosis is strongly suggested; increased human and animal studies are needed to determine the exact role of these factors. Special multiple intervention clinic programs for populations at high risk will be initiated. A US-USSR cooperative risk factor study will be implemented. (For further discussion, see Arteriosclerosis under Research in Chapter III.)

- **Hypertension.** Building on research advances in the genesis of hypertension, a pilot clinical trial for therapy of mild hypertension is proposed. Emphasis will also be expanded on new drug formulations to control hypertension. Hypertension detection and follow-up programs will be continued to determine the effectiveness of therapy. (See Hypertension under Research in Chapter III.)

- **Cerebrovascular Disease.** Animal studies will be initiated to determine the contribution of chronic arteriosclerosis and hypertension to stroke from brain hemorrhage. Other programs will be continued. (See Cerebrovascular Disease under Research in Chapter III.)

- **Arrhythmias.** Fundamental research programs will be expanded to increase our understanding of arrhythmias in order to prevent those which cause sudden cardiac death. Expanded activities will focus particularly on the electrophysiology and therapy of rhythm disturbances, on clinical studies to identify chronic or intermittent disturbances, and on the development of techniques for analyzing electrocardiographic rhythm signals. (See Arrhythmias under Research in Chapter III.)

- **Circulatory Assistance.** The majority of activities in this program area are continuations formerly classified in other program areas, primarily heart failure and shock. Expanded efforts will include development of heart assist and replacement devices. (See Circulatory Assistance under Research in Chapter III.)

- **Structure and Function of the Lung.** Recent research advances at the cellular level hold great promise for understanding the mechanisms involved in the development of lung diseases. Individual and collaborative research efforts will be expanded in order to build on these advances. (See Structure and Function of the Lung under Research in Chapter III.)

- **Pediatric Pulmonary Diseases.** Recent important breakthroughs have occurred which make possible effective detection and therapy of hyaline membrane disease. Plans are being developed for improved management of hyaline membrane disease through programs for rapid transfer of infants with this disease to intensive care units. Programs will be initiated for improved treatment of cystic fibrosis and long-term follow-up of children with bronchiolitis. (See Pediatric Pulmonary Diseases under Research in Chapter III.)

- **National Research and Demonstration Centers.** The Centers will provide an important mechanism by which the Institute can assure that the advances gained through research are translated to improved health care in the community. (See Chapter VI.)

- **Prevention, Control, and Education Programs.** Major program emphases discussed in Chapter III which will necessitate increased support are as follows:

  - Hypertension information and education programs
  - Community hypertension control demonstration projects
  - Increased nutrition and other risk factor detection and prevention efforts related to arteriosclerosis
  - Collaborative emergency care and rehabilitation programs related to coronary heart disease
  - Early recognition and treatment demonstration programs for cardiac and respiratory diseases of the newborn
  - Professional and public educational programs concerning avoidance of noxious dust, vapors, or gases
  - Collaborative education programs related to smokers
  - Education programs for sickle cell disease and Cooley's anemia
  - Screening and education clinics for sickle cell disease

- Education programs in hemophilia

- Hepatitis epidemiology and control programs

- Evaluation of technical, social, ethical, and legal problems associated with organ transplantation

- Professional education regarding optimal use of blood resources.

- **Construction.** Construction of appropriate and adequate facilities will be important to the planned increases in program activity. The projected establishment of National Research and Demonstration Centers in FY 75 particularly requires that additional funds be available. (See Chapter VI.)

- **Manpower.** Funds for the development and maintenance of highly skilled manpower are necessary in order to ensure that well-trained scientists, physicians, and allied health professionals will be available to assume the increased responsibilities inherent in the implementation of a National Program. (See Chapter V.)

NHLI STAFF ALLOCATION PLAN

The Act also requires that the Plan for the National Program include a statement regarding the NHLI staffing needs for implementing the Program. The Institute Summary of May 1973 included such a statement, noting that there were 626 authorized positions for the NHLI at that time and projecting a need for 764 positions in FY 74. As of February 13, 1974, the authorized ceiling for the NHLI is 664 positions. By judicious use of manpower resources, the Institute has been able to initiate activity in several areas in response to the provisions of the Act. Examples, discussed in more detail in other chapters of this report, are cited briefly below:

- Appointment of an Executive Secretary for the National Heart and Lung Advisory Council

- Provision of staff assistance to the Council in its expanded role, particularly in the areas of program planning and preparation of the Annual Report of the Council

- Updating of the National Program Plan and development of this Annual Report of the NHLI

- Organization of the Interagency Technical Committee and staff to provide support for its coordinating role

- Establishment of an Office of Prevention, Control, and Education and planning for prevention, control, and education programs in several areas

- Development and distribution of a Program Announcement and Guidelines for National Research and Demonstration Centers, with first competition for awards underway.

To initiate these programs, the Institute has conserved manpower in a number of ways. One was to abolish the Division of Technological Applications and divide its activities among the three categorical scientific divisions. Another way was to centralize the review function for programs supported by the contract mechanism. A third way was to consolidate some of the intramural activities.

In addition to the above efforts the scientific divisions of the NHLI have formulated plans and begun implementing the Action items in the National Program:

- The Division of Heart and Vascular Diseases will establish Specialized Centers of Research (SCOR) in Ischemic Heart Disease; bring up to full strength the ongoing clinical trials in the areas of risk factor modification, lipid metabolism, and hypertension; expand work on cardiovascular devices, including circulatory assist pumps and noninvasive means for diagnosing heart and blood vessel diseases; and stimulate increased activity in fundamental and clinical research.

- The Division of Lung Diseases will expand programs that apply the fundamental scientific disciplines to research on the normal and diseased lung; initiate and expand epidemiological studies; initiate education and control programs; and expand efforts related to development of life-saving respiratory assist devices. The pace of research in lung diseases, long lagging, is only now entering a phase of rapid acceleration.

- The Division of Blood Diseases and Resources will expand the hemophilia program; take advantage of recently acquired knowledge regarding hepatitis and expand the hepatitis program; stimulate basic and clinical research in bleeding and clotting disorders; and play a major role in the development of the Nationwide Blood Program.

- The Division of Intramural Research will expand laboratories devoted to lung diseases (only recently established), the molecular basis for sickle cell disease and Cooley's anemia, and the molecular basis for certain lipid abnormalities.

- The Division of Extramural Affairs, responsible for initial review of proposals in many of the above areas, of necessity will have to expand as the demand for its services increases.

To operate the National Program effectively, the NHLI will need additional staff--at the middle and upper professional levels as well as in support positions. Programs such as disease prevention, control, and education, and comprehensive centers are new to the Institute. Their review and administration will require staff with knowledge and skills new to the Institute.

Over the years, authorized ceilings for staff for the NHLI have not kept pace with appropriations. In the five years preceding the enactment of Public Law 92-423, the appropriation increased by 38 percent: from $168 million in FY 68 to $232.6 million in FY 72. In the same period, the number of authorized positions increased by only 2.9 percent from 609 to 626. Since the passage of the Act, the obligational authority for the Institute has increased by about 23 percent. If one includes the release of approximately $43 million in impounded FY 73 funds during FY 74, the increase in authority is about 41 percent. During the same period of time, there has been a modest increase in the number of authorized positions to 664. However, during this period there has been an increased emphasis on clinical trials, other collaborative programs, and specialized programs such as Specialized Centers of Research, all of which require a high ratio of manpower to dollar expenditure for effective management and coordination.

The NHLI Summary of May 1973 projected staff needs of 764 in FY 74, up from a base of 626 positions in FY 73, and a further increase to approximately 810 positions in FY 76. Our current position ceiling is 664 for FY 74 and the same number for FY 75. These position allocations are substantially below our estimates of staffing needs for the program outlined in this report, even in view of the above-mentioned efforts to conserve manpower.

APPENDIX A

NATIONAL HEART, BLOOD VESSEL, LUNG, AND BLOOD ACT OF 1972

APPENDIX A

NATIONAL HEART, BLOOD VESSEL, LUNG, AND BLOOD ACT OF 1972

Public Law 92-423
92nd Congress, S. 3323
September 19, 1972

An Act

To amend the Public Health Service Act to enlarge the authority of the National Heart and Lung Institute in order to advance the national attack against diseases of the heart and blood vessels, the lungs, and blood, and for other purposes.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled.

National Heart, Blood Vessel, Lung, and Blood Act of 1972.

SHORT TITLE

SECTION 1. This Act may be cited as the "National Heart, Blood Vessel, Lung, and Blood Act of 1972".

FINDINGS AND DECLARATION OF PURPOSE

SEC. 2. (a) Congress finds and declares that—

(1) diseases of the heart and blood vessels collectively cause more than half of all the deaths each year in the United States and the combined effect of the disabilities and deaths from such diseases is having a major social and economic impact on the Nation;

(2) elimination of heart and blood vessel diseases as significant causes of disability and death could increase the average American's life expectancy by about eleven years and could provide for annual savings to the economy in lost wages, productivity, and costs of medical care of more than $30,000,000,000 per year;

(3) chronic lung diseases have been gaining steadily in recent years as important causes of disability and death, with emphysema alone being the fastest rising cause of death in the United States;

(4) chronic respiratory diseases affect an estimated ten million Americans, emphysema an estimated one million, chronic bronchitis an estimated four million, and asthma an estimated five million;

(5) thrombosis (the formation of blood clots in the vessels) may cause, directly or in combination with other problems, many deaths and disabilities from heart disease and stroke which can now be prevented;

86 STAT. 679

86 STAT. 680

(6) blood and blood products are essential human resources whose value in saving life and promoting health cannot be assessed in terms of dollars;

(7) the provision of prompt and effective emergency medical services utilizing to the fullest extent possible advances in transportation and communications and other electronic systems and specially trained professional and paraprofessional health care personnel can reduce substantially the number of fatalities and severe disabilities due to critical illnesses in connection with heart, blood vessel, lung, and blood diseases; and

(8) the greatest potential for advancement against heart, blood vessel, lung, and blood diseases lies in the National Heart and Lung Institute, but advancement against such diseases depends not only on the research programs of that Institute but also on the research programs of other research institutes of the National Institutes of Health.

(b) It is the purpose of this Act to enlarge the authority of the National Heart and Lung Institute in order to advance the national attack upon heart, blood vessel, lung, and blood diseases.

83-749 O (260)

HEART, BLOOD VESSEL, LUNG, AND BLOOD DISEASE PROGRAMS

62 Stat. 464. 42 USC 287-287c.

SEC. 3. Part B of title IV of the Public Health Service Act is amended (1) by redesignating section 413 as section 419A. (2) by redesignating section 414 as section 418, and (3) by adding after section 412 the following new sections:

"NATIONAL HEART, BLOOD VESSEL, LUNG, AND BLOOD DISEASE PROGRAM

"SEC. 413. (a) The Director of the Institute, with the advice of the Council, shall develop a plan for a National Heart, Blood Vessel, Lung, and Blood Disease Program (hereafter in this part referred to as the 'Program') to expand, intensify, and coordinate the activities of the Institute respecting heart, blood vessel, lung, and blood diseases (including its activities under section 412) and shall carry out the Program in accordance with such plan. The Program shall be coordinated with the other research institutes of the National Institutes of Health to the extent that they have responsibilities respecting such diseases and shall provide for—

NIH, coordination provisions.

"(1) investigation into the epidemiology, etiology, and prevention of all forms and aspects of heart, blood vessel, lung, and blood diseases, including investigations into the social, environmental, behavioral, nutritional, biological, and genetic determinants and influences involved in the epidemiology, etiology, and prevention of such diseases;

"(2) studies and research into the basic biological processes and mechanisms involved in the underlying normal and abnormal heart, blood vessel, lung, and blood phenomena;

"(3) research into the development, trial, and evaluation of techniques, drugs, and devices (including computers) used in, and approaches to, the diagnosis, treatment (including emergency medical service), and prevention of heart, blood vessel, lung, and blood diseases and the rehabilitation of patients suffering from such diseases;

86 STAT. 680
86 STAT. 681

"(4) establishment of programs that will focus and apply scientific and technological efforts involving biological, physical, and engineering sciences to all facets of heart, blood vessel, lung, and blood diseases with emphasis on refinement, development, and evaluation of technological devices that will assist, replace, or monitor vital organs and improve instrumentation for detection, diagnosis, and treatment of those diseases;

"(5) establishment of programs for the conduct and direction of field studies, large-scale testing and evaluation, and demonstration of preventive, diagnostic, therapeutic, and rehabilitative approaches to, and emergency medical services for, such diseases;

"(6) studies and research into blood diseases and blood, and into the use of blood for clinical purposes and all aspects of the management of its resources in this country, including the collection, preservation, fractionalization, and distribution of it and its products;

"(7) the education and training of scientists, clinicians, and educators, in fields and specialties (including computer sciences) requisite to the conduct of programs respecting heart, blood vessel, lung, and blood diseases;

"(8) public and professional education relating to all aspects of such diseases and the use of blood and blood products and the management of blood resources;

"(9) establishment of programs for study and research into heart, blood vessel, lung, and blood diseases of children (including cystic fibrosis, hyaline membrane, and hemolytic and hemophilic

diseases) and for the development and demonstration of diagnostic, treatment, and preventive approaches to these diseases; and

"(10) establishment of programs for study, research, development, demonstrations and evaluation of emergency medical services for people who become critically ill in connection with heart, blood vessel, lung, or blood diseases, which programs shall include programs for (A) the training of paraprofessionals in (i) emergency treatment procedures, and (ii) utilization and operation of emergency medical equipment, (B) the development and operation of (i) mobile critical care units (including helicopters and other airborne units where appropriate), (ii) radio, telecommunications, and other means of communications, and (iii) electronic monitoring systems, and (C) the coordination with other community services and agencies in the joint use of all forms of emergency vehicles, communications systems, and other appropriate services.

The Program shall give special emphasis to the continued development in the Institute of programs relating to atherosclerosis, hypertension, thrombosis, and congenital abnormalities of the blood vessels as causes of stroke, and to effective coordination of such programs with related stroke programs in the National Institute of Neurological Diseases and Stroke. National Institute of Neurological Diseases and Stroke, coordination.

"(b)(1) The plan required by subsection (a) of this section shall (A) be developed within one hundred and eighty days after the effective date of this section, (B) be transmitted to the Congress, and (C) set out the Institute's staff requirements to carry out the Program and recommendations for appropriations for the Program. Plan development; transmittal to Congress. 86 STAT. 681 86 STAT. 682

"(2) The Director of the Institute shall, as soon as practicable after the end of each calendar year, prepare in consultation with the Council and submit to the President for transmittal to the Congress a report on the activities, progress, and accomplishments under the Program during the preceding calendar year and a plan for the Program during the next five years. Report to President, transmittal to Congress.

"(c) In carrying out the Program, the Director of the Institute, under policies established by the Director of the National Institutes of Health and after consultation with the Council and without regard to any other provision of this Act, may— Director, functions.

"(1) if authorized by the Council, obtain (in accordance with section 3109 of title 5, United States Code, but without regard to the limitation in such section on the number of days or the period of such service) the services of not more than fifty experts or consultants who have scientific or professional qualifications; 80 Stat. 416.

"(2) acquire, construct, improve, repair, operate, and maintain heart, blood vessel, lung, and blood disease laboratory, research, training, and other necessary facilities and equipment, and related accommodations as may be necessary, and such other real or personal property (including patents) as the Director deems necessary; and acquire, without regard to the Act of March 3, 1877 (40 U.S.C. 34), by lease or otherwise, through the Administrator of General Services, buildings or parts of buildings in the District of Columbia or communities located adjacent to the District of Columbia for the use of the Institute for a period not to exceed ten years; and 19 Stat. 370.

"(3) enter into such contracts, leases, cooperative agreements, or other transactions, without regard to sections 3648 and 3709 of the Revised Statutes of the United States (31 U.S.C. 529, 41 U.S.C. 5), as may be necessary in the conduct of his functions, with any public agency, or with any person, firm, association, corporation, or educational institution.

Assistant Director for Health Information Programs.
Cardiovascular and pulmonary diseases, information.

"(d) There shall be in the Institute an Assistant Director for Health Information Programs who shall be appointed by the Director of the Institute. The Director of the Institute, acting through the Assistant Director for Health Information Programs, shall conduct a program to provide the public and the health professions with health information with regard to cardiovascular and pulmonary diseases. In the conduct of such program, special emphasis shall be placed upon dissemination of information regarding diet, exercise, stress, hypertension, cigarette smoking, weight control, and other factors affecting the prevention of arteriosclerosis and other cardiovascular diseases and of pulmonary diseases.

"HEART, BLOOD VESSEL, LUNO, AND BLOOD DISEASE PREVENTION AND CONTROL PROGRAMS

"SEC. 414. (a) The Director of the Institute, under policies established by the Director of the National Institutes of Health and after consultation with the Council, shall establish programs as necessary for cooperation with other Federal Health agencies, State, local, and regional public health agencies, and nonprofit private health agencies in the diagnosis, prevention, and treatment (including the provision of emergency medical services) of heart, blood vessel, lung, and blood diseases, appropriately emphasizing the prevention, diagnosis, and treatment of such diseases of children.

86 STAT. 682
86 STAT. 683

Appropriations.

"(b) There is authorized to be appropriated to carry out this section $25,000,000 for the fiscal year ending June 30, 1973, $35,000,000 for the fiscal year ending June 30, 1974, and $45,000,000 for the fiscal year ending June 30, 1975.

"NATIONAL RESEARCH AND DEMONSTRATION CENTERS FOR HEART, BLOOD VESSEL, LUNO, AND BLOOD DISEASES

"SEC. 415. (a) (1) The Director of the Institute may provide for the development of—

"(A) fifteen new centers for basic and clinical research into, training in, and demonstration of, advanced diagnostic, prevention, and treatment methods (including methods of providing emergency medical services) for heart, blood vessel, and blood diseases; and

"(B) fifteen new centers for basic and clinical research into, training in, and demonstration of, advanced diagnostic, prevention, and treatment methods (including methods of providing emergency medical services) for chronic lung diseases (including bronchitis, emphysema, asthma, cystic fibrosis, and other lung diseases of children).

"(2) The centers developed under paragraph (1)(A) shall, in addition to being utilized for research, training, and demonstrations, be utilized for the following prevention programs for cardiovascular diseases:

"(A) Programs to develop improved methods of detecting individuals with a high risk of developing cardiovascular disease.

"(B) Programs to develop improved methods of intervention against those factors which cause individuals to have a high risk of developing such disease.

"(C) Programs to develop health professions and allied health professions personnel highly skilled in the prevention of such disease.

"(D) Programs to develop improved methods of providing emergency medical services for persons with such disease.

"(3) Centers developed under this subsection may be supported under subsection (b) or under any other applicable provision of law. The research, training, and demonstration activities carried out through any such center may relate to any one or more of the diseases referred to in paragraph (1) of this subsection.

"(b) The Director of the Institute, under policies established by the Director of the National Institutes of Health and after consultation with the Council, may enter into cooperative agreements with public or nonprofit private agencies or institutions to pay all or part of the cost of planning, establishing, or strengthening, and providing basic operating support for, existing or new centers (including centers established under subsection (a)) for basic or clinical research into, training in, and demonstration of, advanced diagnostic, prevention, and treatment methods for heart, blood vessel, lung, or blood diseases. Funds paid to centers under cooperative agreements under this subsection may be used for— Public or non-profit agencies, cooperative agreements. Use of funds.

"(1) construction, notwithstanding section 405, 58 Stat. 708.

"(2) staffing and other basic operating costs, including such patient care costs as are required for research, 42 USC 285. 86 STAT. 683

"(3) training, including training for allied health professions personnel, and 86 STAT. 684

"(4) demonstration purposes.

The aggregate of payments (other than payments for construction) made to any center under such an agreement may not exceed $5,000,000 in any year. Support of a center under this subsection may be for a period of not to exceed five years and may be extended by the Director of the Institute for additional periods of not more than five years each, after review of the operations of such center by an appropriate scientific review group established by the Director. As used in this section, the term 'construction' does not include the acquisition of land. Limitations. "Construction."

"INTERAGENCY TECHNICAL COMMITTEE

"SEC. 416. (a) The Secretary shall establish an Interagency Technical Committee on Heart, Blood Vessel, Lung and Blood Diseases and Blood Resources which shall be responsible for coordinating those aspects of all Federal health programs and activities relating to heart, blood vessel, lung, and blood diseases and to blood resources to assure the adequacy and technical soundness of such programs and activities and to provide for the full communication and exchange of information necessary to maintain adequate coordination of such programs and activities. Establishment.

"(b) The Director of the Institute shall serve as Chairman of the Committee and the Committee shall include representation from all Federal departments and agencies whose programs involve health functions or responsibilities as determined by the Secretary.

"NATIONAL HEART AND LUNG ADVISORY COUNCIL

"SEC. 417. (a) There is established in the Institute a National Heart and Lung Advisory Council to be composed of twenty-three members as follows: Establishment; membership.

"(1) The Secretary, the Director of the National Institutes of Health, the Director of the Office of Science and Technology, and the chief medical officer of the Veterans' Administration (or their designees), and a medical officer designated by the Secretary of Defense, shall be ex officio members of the Council.

"(2) Eighteen members appointed by the Secretary.

Eleven of the appointed members shall be selected from among the leading medical or scientific authorities who are skilled in the sciences

relating to diseases of the heart, blood vessels, lungs, and blood; two of the appointed members shall be selected from persons enrolled in residency programs providing training in heart, blood vessel, lung, or blood diseases; and five of the appointed members shall be selected from members of the general public who are leaders in the fields of fundamental or medical sciences or in public affairs.

Terms.

"(b)(1) Each appointed member of the Council shall be appointed for a term of four years, except that—

"(A) any member appointed to fill a vacancy occurring prior to the expiration of the term for which his predecessor was appointed shall be appointed for the remainder of such term; and

86 STAT. 684
86 STAT. 685

"(B) of the members first appointed after the effective date of this section, five shall be appointed for a term of four years, five shall be appointed for a term of three years, five shall be appointed for a term of two years, and three shall be appointed for a term of one year, as designated by the Secretary at the time of appointment.

Extension.

Appointed members may serve after the expiration of their terms until their successors have taken office.

"(2) A vacancy in the Council shall not affect its activities, and twelve members of the Council shall constitute a quorum.

National Advisory Heart Council, replacement provisions.
64 Stat. 446.
42 USC 218.

"(3) The Council shall supersede the existing National Advisory Heart Council appointed under section 217, and the appointed members of the National Advisory Heart Council serving on the effective date of this section shall serve as additional members of the National Heart and Lung Advisory Council for the duration of their terms then existing, or for such shorter time as the Secretary may prescribe.

"(4) Members of the Council who are not officers or employees of the United States shall receive for each day they are engaged in the performance of the functions of the Council compensation at rates not to exceed the daily equivalent of the annual rate in effect for grade GS–18 of the General Schedule, including traveltime; and all members, while so serving away from their homes or regular places of business, may be allowed travel expenses, including per diem in lieu of subsistence, in the same manner as such expenses are authorized by section 5703 of title 5, United States Code, for persons in the Government service employed intermittently.

5 USC 5332 note.

80 Stat. 499; 83 Stat. 190.

"(c) The Secretary (or his designee) shall be the Chairman of the Council.

Executive Secretary.

"(d) The Director of the Institute shall (1) designate a member of the staff of the Institute to act as Executive Secretary of the Council, and (2) make available to the Council such staff, information, and other assistance as it may require to carry out its functions.

"(e) The Council shall meet at the call of the Chairman, but not less often than four times a year."

AUTHORIZATION OF APPROPRIATIONS FOR PART B OF TITLE IV OF THE PUBLIC HEALTH SERVICE ACT

Ante, p. 680.

SEC. 4. Part B of title IV of the Public Health Service Act is amended by adding at the end thereof the following new section:

"AUTHORIZATION OF APPROPRIATIONS

Ante, p. 682.

"SEC. 419B. For the purpose of carrying out this part (other than section 414), there is authorized to be appropriated $375,000,000 for the fiscal year ending June 30, 1973, $425,000,000 for the fiscal year ending June 30, 1974, and $475,000,000 for the fiscal year ending June 30, 1975. Of the sums appropriated under thia section for any fiscal year, not less than 15 per centum of such sums shall be reserved

for programs under this part respecting diseases of the lung and not less than 15 per centum of such sums shall be reserved for programs under this part for programs respecting diseases of the blood."

AUTHORITY OF THE DIRECTOR OF THE NATIONAL HEART AND LUNG INSTITUTE TO APPROVE GRANTS

SEC. 5. Section 419A of the Public Health Service Act (as so redesignated by section 3 of this Act) is amended—

(1) by striking out "grants-in-aid" in subsection (a) and inserting in lieu thereof "except as provided in subsection (c), grants-in-aid"; and

(2) by adding after subsection (b) the following new subsection:

"(c) Under procedures approved by the Director of the National Institutes of Health, the Director of the National Heart and Lung Institute may approve grants under this Act for research and training in heart, blood vessel, lung, and blood diseases—

"(1) in amounts not to exceed $35,000 after appropriate review for scientific merit but without review and recommendation by the Council, and Limitations.

"(2) in amounts exceeding $35,000 after appropriate review for scientific merit and recommendation for approval by the Council."

CONFORMING AMENDMENTS TO PART B OF TITLE IV OF THE PUBLIC HEALTH SERVICE ACT

SEC. 6. (a) Section 411 of the Public Health Service Act is amended by striking out "National Heart Institute" and inserting in lieu thereof "National Heart and Lung Institute". 62 Stat. 465. 42 USC 287.

(b) Section 412 of such Act is amended— 42 USC 287a.

(1) by striking out "heart" each place it occurs (except in the heading) and inserting in lieu thereof "heart, blood vessel, lung, and blood";

(2) by striking out "Surgeon General" and inserting in lieu thereof "Secretary";

(3) by striking out "National Advisory Heart Council" and inserting in lieu thereof "National Heart and Lung Advisory Council";

(4) by redesignating paragraphs (a), (b), (c), (d), (e), (f), and (g) as paragraphs (1), (2), (3), (4), (5), (6), and (7), respectively; and

(5) by amending the section heading to read as follows:

"RESEARCH AND TRAINING IN DISEASES OF THE HEART, BLOOD VESSELS, LUNG, AND BLOOD"

(c) Section 418 of such Act (as so redesignated by section 3 of this Act) is amended—

(1) by inserting "(a)" immediately after "SEC. 418." and by adding at the end thereof the following new subsection:

"(b)(1) The Council shall advise and assist the Director of the Institute with respect to the Program established under section 413. The Council may hold such hearings, take such testimony, and sit and act at such times and places, as the Council deems advisable to investigate programs and activities of the Program. Ante, p. 680.

"(2) The Council shall submit a report to the President for transmittal to the Congress not later than January 31 of each year on the progress of the Program toward the accomplishment of its objectives." Report to President, transmittal to Congress.

(2) by striking out "Surgeon General" each place it occurs (except paragraph (f)) and inserting in lieu thereof "Secretary";

(3) by striking out "heart" each place it occurs and inserting in lieu thereof "heart, blood vessel, lung, and blood";

(4) by striking out "Surgeon General" in paragraph (f) and inserting in lieu thereof "Secretary, the Director of the National Institutes of Health, and the Director of the National Heart and Lung Institute"; and

(5) by redesignating paragraphs (a), (b), (c), (d), (e), and (f) as paragraphs (1), (2), (3), (4), (5), and (6), respectively.

(d) Section 419A of such Act (as so redesignated by section 3 of this Act) is amended—

(1) in subsection (a), by (A) striking out "Surgeon General" and inserting in lieu thereof "Secretary", and (B) striking out "heart" and inserting in lieu thereof "heart, blood vessel, lung, and blood"; and

(2) in subsection (b), by (A) striking out "The Surgeon General shall recommend to the Secretary acceptance of conditional gifts, pursuant to section 501," and inserting in lieu thereof "The Secretary may, in accordance with section 501, accept conditional gifts", and (B) striking out "heart" and inserting in lieu thereof "heart, blood vessel, lung, and blood".

58 Stat. 709.
42 USC 219.

(e) The heading for part B of such Act is amended to read as follows:

"PART B—NATIONAL HEART AND LUNG INSTITUTE".

CONFORMING AMENDMENTS TO OTHER PROVISIONS OF THE PUBLIC HEALTH SERVICE ACT

SEC. 7. (a) Section 217 of such Act is amended—

64 Stat. 446.
42 USC 218.

(1) by striking out "the National Advisory Heart Council," each place it occurs in subsection (a);

(2) by striking out "heart diseases," in subsection (a) and by striking out "heart," in subsection (b).

58 Stat. 692;
62 Stat. 601;
79 Stat. 448.
42 USC 241.

(b) Sections 301(d) and 301(i) of such Act are each amended by striking out "National Advisory Heart Council" and inserting in lieu thereof "National Heart and Lung Advisory Council".

REPORT TO CONGRESS

Review.

SEC. 8. The Secretary of Health, Education, and Welfare shall carry out a review of all administrative processes under which the National Heart, Blood Vessel, Lung, and Blood Disease Program, established under part B of title IV of the Public Health Service Act, will operate, including the processes of advisory council and peer group reviews, in order to assure the most expeditious accomplishment of the objectives of the Program. Within one year of the date of enactment of this Act, the Secretary shall submit a report to the Congress of the findings of such review and the actions taken to facilitate the conduct of the Program, together with recommendations for any needed legislative changes.

Ante, p. 680.

EFFECTIVE DATE

SEC. 9. This Act and the amendments made by this Act shall take effect sixty days after the date of enactment of this Act or on such prior date after the date of enactment of this Act as the President shall prescribe and publish in the Federal Register. Publication in Federal Register.

Approved September 19, 1972.

LEGISLATIVE HISTORY:

HOUSE REPORTS: No. 92-1108 accompanying H.R. 15081 (Comm. on Interstate and Foreign Commerce) and No. 92-1349 (Comm. of Conference).
SENATE REPORTS: No. 92-733 (Comm. on Labor and Public Welfare) and No. 92-1068 (Comm. of Conference).
CONGRESSIONAL RECORD, Vol. 118 (1972):
Apr. 7, considered and passed Senate.
July 18, considered and passed House, amended, in lieu of H.R. 15081.
Aug. 16, House agreed to conference report.
Sept. 6, Senate agreed to conference report.
WEEKLY COMPILATION OF PRESIDENTIAL DOCUMENTS, Vol. 8, No. 39:
Sept. 20, Presidential statement.

APPENDIX B

DEFINITION OF MAJOR PROBLEM AREAS

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DEFINITION OF MAJOR PROBLEM AREAS

The major problem areas addressed by the National Heart, Blood Vessel, Lung, and Blood Act of 1972 are heart and blood vessel diseases, lung diseases, and blood diseases and blood resources. This appendix includes for each major problem area definitions of the disease problems covered by the program, discussion of the relationship of the disease problem to other diseases and/or disorders, and statistical data on the impact and scope of the disease problem in the United States. This appendix is reprinted directly from Section II, Volume I, the National Heart and Lung Institute Summary (May 1, 1973) of the National Heart, Blood Vessel, Lung, and Blood Program. Two additional lung disease problems, which have been designated major problem areas in the updated 5-year Plan, have been added at the end. Circulatory Assistance, Respiratory Assistance, and Biomaterials are not disease problem areas. However, they constitute three of the 22 major program elements and play important roles in the treatment of several of the major diseases in the National Program. A brief definition of each has also been added to this appendix.

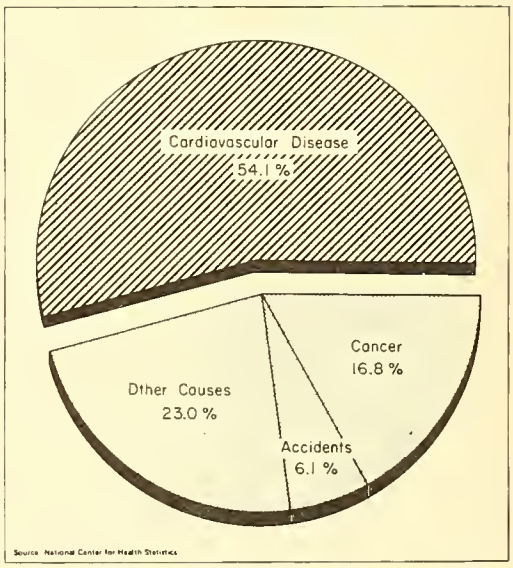
DEFINITION OF MAJOR PROBLEM AREAS

The four major problem areas covered by the National Heart, Blood Vessel, Lung and Blood Act are discussed separately in the following three sections: Heart and Blood Vessel Diseases, Lung Diseases, Blood Diseases and Blood Resources. As pointed out in the Report of the Panel Chairmen, there are many interrelationships among these problem areas. The Chairmen state: "Disordered biological functions seldom involve a single area. As examples, pulmonary embolism begins with thrombosis and involves the lung and its circulation as well as the heart. Effective delivery of oxygen to the tissue depends on the lung, the heart, the amount, type, and functional states of the hemoglobin, and the peripheral circulation."

HEART AND BLOOD VESSEL DISEASES

For more than fifty years, heart and blood vessel diseases have been the major cause of death in this country. They now account for 54 percent of all deaths annually (Figure 2). This is more than three times the death rate from cancer, the next highest cause. An estimated 28 million Americans have diseases of the heart and blood vessels, resulting in a large burden of acute and chronic illness and disability. Hence, there is reason for referring to heart and blood vessel diseases as the modern epidemic. Moreover, heart and blood vessel diseases cost the economy more than $30 billion per year in wages, lost productivity, and expenses for medical care.

Figure 2
DEATHS FROM ALL CAUSES
UNITED STATES, 1967



Nine major problem areas in heart and blood vessel diseases are defined below: Arteriosclerosis, Hypertension, Cerebrovascular Disease, Coronary Heart Disease, Peripheral Vascular Diseases, Arrhythmias, Heart Failure and Shock, Congenital and Rheumatic Heart Diseases, and Cardiomyopathy and Infections of the

Heart. Of these, arteriosclerosis and hypertension are considered the major cardiovascular disease problems in the United States. The causes of arteriosclerosis and most cases of hypertension are unknown.

Arteriosclerosis, or "hardening of the arteries," is responsible for 84 percent of the deaths from heart and blood vessel diseases. It is a chronic pathological change in the blood vessels and its most common form is atherosclerosis in which the inner lining of the arteries becomes rough, thick, hard and covered with plaques. Eventually, the inner diameter of the vessels decreases and blood flow in the diseased arteries diminishes or stops completely. Atherosclerosis begins early in life and is asymptomatic for years. Virtually all adult American males, and post-menopausal women, are afflicted to some degree. The disease manifests itself in many ways, but primarily as heart attacks, strokes and occlusive disease of the peripheral vessels. Therefore, if arteriosclerosis could be prevented, hundreds of thousands of lives might be prolonged. International statistics reveal a great variation in death rates for coronary heart disease. For instance, in Denmark, Norway, and Sweden, the death rate for men under the age of 55 is less than half that for the same age group in the United States. This difference indicates that the high death rates due to arteriosclerosis in the United States are neither necessary nor inevitable.

Hypertension, or high blood pressure, is one of the most commonly encountered forms of heart and blood vessel diseases, affecting an estimated 23 million adult Americans, or between 10 and 15 percent of the population. High blood pressure is the most important factor contributing to the development of strokes. It also accelerates the development of atherosclerosis in the coronary and peripheral vessels. Control of hypertension would, therefore, reduce the incidence of three major causes of death and disability: stroke, coronary heart disease and peripheral vascular disease. High blood pressure is easy to detect, but may exist for many years without symptoms. It can be controlled with presently available therapy. However, of the millions of Americans with this disease, one half are probably unaware that they have it, and of those who are aware, less than one half are receiving adequate therapy. Although hypertension is widely distributed among Americans, it has been found to be more common and severe among the black population.

Cerebrovascular Disease occurs when an artery supplying blood to the brain is blocked, ruptured, or injured. Cerebrovascular disease due to arteriosclerosis and especially due to hypertension is the basis for the great majority of strokes. The individual and public health burden of death, paralysis and brain damage is large. Of the 1.7 million adults who have this disease, 700,000 are partially or completely disabled. Stroke kills about 200,000 persons a year, more men than women, and at a greater rate among blacks than whites. Each year, some 530,000 patients are discharged from our hospitals with a diagnosis of stroke, and each year about 250,000 individuals, between the ages of 25 and 64, are crippled mentally or physically by a stroke. Many more lives could be saved and disabilities prevented if we had effective methods for prevention and treatment of arteriosclerosis and hypertension and if available treatment were more widely applied. It should be noted that, due to the recent advances in therapy for high blood pressure, there has been an appreciable long-term decrease in deaths from stroke.

Coronary Heart Disease refers to atherosclerosis in the arteries that supply the heart muscle. A heart attack is a manifestation of coronary heart disease and occurs when a coronary artery is blocked, preventing the blood from reaching the heart muscle. This produces death of the heart muscle, technically called myocardial infarction. Coronary heart disease is the major manifestation of atherosclerosis. It is the predominant form of heart disease in the adult American and causes 1.25 million heart attacks a year, and is responsible for chronic illness in 4 million Americans, 2.5 million below the age of 65. In 1969, coronary heart disease accounted for about 675,000 deaths in this country. It is the largest single cause of death from cardiovascular disease and is the leading cause of death in both men and women. Each year, approximately 130,000 persons in their most productive years (below age 65) die of coronary heart disease.

Coronary heart disease may also result in angina pectoris (a pain usually located in the chest and arm that is brought on by exercise, exposure to cold, and other factors), heart failure (impaired pumping performance of the heart leading to accumulation of fluid in the body and congestion in the lungs), disturbances of heart rhythm and sudden death. Each year, 400,000 deaths from coronary heart disease occur suddenly or before hospitalization. Half of these occur instantaneously and unwitnessed. Either heart disease or hypertension is evident in 300,000 of these cases, but in 100,000, sudden cardiac death is the first evidence of heart disease.

Peripheral Vascular Diseases are abnormalities that occur within arteries or veins. Atherosclerotic narrowing may result in inadequate blood flow through the

arteries. The veins may become dilated (varicosities) or inflamed and obstructed by blood clots (thrombophlebitis). These diseases may be painful and result in organ damage, skin ulcerations and gangrene. Peripheral vascular diseases are a significant cause of disability and illness. For example, peripheral vascular disease in the legs may affect one's ability to walk or run. Thrombosis in the veins may produce pulmonary embolism; i.e., clot fragments may be carried in the blood from their site of origin to the lungs. This in turn may result in shock and death. Leg vein thrombosis is the cause of more than 90 percent of pulmonary emboli which in turn are responsible for approximately 50,000 deaths a year in this country. About 265,000 patients are discharged from our hospitals each year with a primary diagnosis of peripheral vascular disease.

Arrhythmias, or abnormal heart rhythms, occur with many forms of heart disease and result from an alteration in the normal transmission of electrical impulses within the heart. They may also occur without recognizable disease. Many rhythm disturbances have minor influence upon life expectancy and cause little disability, others cause serious symptoms, and some are almost instantaneously fatal. For example, arrhythmias kill more than half of the patients with coronary heart disease and are a major problem in patients with rheumatic heart disease.

Heart Failure and Shock represent major causes of death and may be the end result of many different diseases. Heart failure occurs when the heart has been damaged so extensively that its ability to pump blood is impaired and it can no longer meet the needs of the body. In its chronic form, it is often associated with shortness of breath, accumulation of fluids and swelling of the legs. Shock is also a secondary phenomenon characterized by an inability of the heart and peripheral circulation to maintain adequate blood pressure or blood perfusion. Left untreated, it rapidly leads to irreversible damage to the tissues, and to death. Shock can be a complication of many disorders such as heart attacks, hemorrhage, or burns and stroke.

Heart failure and shock are the primary causes of in-hospital deaths from heart attack and most other types of heart disease, thus accounting for over a quarter million deaths annually. In addition, chronic heart failure may follow a heart attack or result from high blood pressure or other heart diseases. Over two million Americans have chronic heart failure, and each year the total cost of their hospitalization exceeds $500 million. In the majority, symptoms can be relieved by drugs.

Congenital and Rheumatic Heart Diseases are important diseases of children. Congenital heart disease occurs when the heart or major blood vessels near the heart fail to mature normally before birth. About eight out of every 1,000 children are born with this disease, and half of them do not survive until their first birthday. The causes of congenital heart diseases are generally unknown. Less than 3 percent are known to be related to a particular event or disorder occurring during pregnancy, such as rubella infection or the use of certain drugs, such as thalidomide. Rheumatic fever and rheumatic heart disease were once considered leading causes of childhood illnesses. They can now be prevented. Rheumatic fever is almost always preceded by a streptococcal infection and may lead to damage of the heart valves, thus causing rheumatic heart disease. Rheumatic fever afflicts about 100,000 school children. Both congenital and rheumatic heart diseases cause substantial impairment of health in children, and in adults in their most productive years. They annually cause over 8,000 and 15,000 deaths, respectively, in the United States. The cost of physician care alone for patients with rheumatic fever and rheumatic heart disease was about $28 million in 1969.

Cardiomyopathy and Infections of the Heart are diseases of the heart muscle and its linings. These diseases cause enlargement of the heart, heart failure, irregularities of the heart rhythm, and occasionally sudden death. They are the result of a variety of factors. Known factors include toxic substances, viral infections, alcohol, immunological phenomena, nutritional deficiencies, muscular dystrophy, and a number of rare diseases. The condition may be acute or chronic and progressive. Rapidly fatal disease may be associated with heart failure, disturbances of rhythm and sudden death. Infections may affect the heart muscle (myocarditis), its interior wall (endocarditis), or its exterior surface (pericarditis). Cardiomyopathies, myocarditis, endocarditis, and pericarditis are increasing in frequency. However, quantitative information concerning the prevalence of these diseases is not available because we still lack specific diagnostic criteria and laboratory tests.

LUNG DISEASES

The National Heart, Blood Vessel, Lung and Blood Program encompasses respiratory diseases exclusive of cancer of the lung, upper respiratory infections and pulmonary tuberculosis.

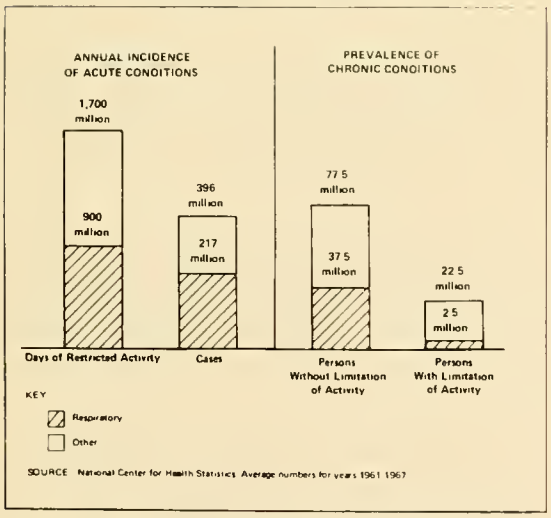
Respiratory diseases that represent national health problems include chronic obstructive pulmonary dis-

eases (COPD), acute respiratory distress syndromes (RDS), and interstitial lung diseases. The economic cost of these diseases has been estimated at $6.3 billion per year.

Lung diseases afflict both the young and the old. In the newborn, the most common cause of death is the respiratory distress syndrome which affects between 50,000 and 100,000 babies in the United States each year, about half of whom die. RDS is implicated in the development of adult respiratory diseases as well. Interstitial lung diseases are a major cause of lung problems in the young adult, and may cause COPD. Of the adult respiratory diseases, emphysema and chronic bronchitis are the major causes of death. An estimated 10 million Americans are currently affected by these diseases, together with asthma. Emphysema and chronic bronchitis represent a particularly pressing health problem since the death rate and prevalence of these conditions have been increasing at an alarming rate over the past 15 years.

As a disabling disease, emphysema is second only to heart disease. The illness and disability caused by respiratory diseases are summarized in Figure 3.

Figure 3
ILLNESS AND DISABILITY FROM RESPIRATORY DISEASES IN THE UNITED STATES



Four major lung disease problems are defined below: Pediatric Pulmonary Diseases, Emphysema and Chronic Bronchitis, Fibrotic and Immunologic Lung Diseases and Respiratory Failure.

Pediatric Pulmonary Diseases present health problems of national dimensions. Hyaline membrane disease (respiratory distress syndrome of the newborn), cystic fibrosis (an inherited disease of abnormal mucus secretion), and bronchiolitis (acute airway obstruction in young children) are among the most important disorders of childhood that involve the lung and the airways. About 40,000 babies are born each year with hyaline membrane disease. More than half of these will die unless given prompt treatment, presently unavailable except in a few specialized facilities.

Cystic fibrosis occurs in about one of every 2,000 live births and approximately 5 percent of the general population in the United States carries the gene for this disorder. Cystic fibrosis is one of the main causes of chronic illness in children and young adults and accounts for most of the deaths from pulmonary disease in the pediatric age group. Bronchiolitis is a common pediatric disorder, but data are not available on its incidence.

Emphysema and Chronic Bronchitis are among the major causes of mortality and illness from pulmonary diseases. Emphysema is a disease in which the thin walls in the alveoli (air sacs) lose their elasticity and tear. Chronic bronchitis refers to a persistent inflammation of the lungs characterized by recurrent coughing and excess mucus in the airways. These diseases may be associated with certain risk factors, such as cigarette smoking, and in some cases with genetic determinants (e.g., deficiency of $alpha_1$-antitrypsin enzyme). Emphysema is a leading cause of death in this country and an even greater cause of disability. Data from 1967 indicate that chronic bronchitis and emphysema account for half of the total 181,000 man-years lost due to lung diseases. The death rate for chronic bronchitis increased by 80 percent between 1958 and 1967. The death rate for emphysema increased by 172 percent in the same period to a level of 10.6 per 100,000 population.

Fibrotic and Immunologic Lung Diseases are induced by many disease factors. Fibrotic responses (proliferation of connective tissue or scar formation) and immunologic responses are characteristic of a variety of lung diseases. Among the factors that may induce these responses are exposure to substances such as coal dust, silica, and asbestos in the environment; viral and bacterial infections; diseases of the connective tissue such as rheumatoid arthritis, lupus, and scleroderma; radiation damage; and exposure to substances like molds and dust that initiate hypersensitivity reactions. Diseases characterized by pulmonary fibrosis and/or

immunologic reactions include pneumoconiosis, sarcoidosis, diffuse hypersensitivity pneumonitis, Farmer's lung and bronchial asthma. This group of lung diseases is a major national health problem, second in magnitude among lung diseases only to emphysema and chronic bronchitis.

Statistical data on fibrotic lung diseases are inadequate because these diseases are difficult to diagnose and poorly reported. However, their national health impact is far greater than is generally appreciated. For example, sarcoidosis is about 12 to 15 times more common among blacks than among whites in this country, and now outranks tuberculosis as a cause of disability from pulmonary insufficiency in black populations. It is also more common in women.

Among immunologic lung diseases, asthma is the most common, affecting about 8.6 million persons in this country (approximately 4 percent of the population). It is responsible for 5 percent of all chronic disabilities and causes an annual loss of about 7 million work-days. Other immunologic lung diseases are associated with specific occupations where exposure to organic dusts or molds is high; for example, Farmer's lung in the north central states, Bagassosis among sugar cane workers in the south, and hypersensitivity pneumonitis from organisms growing in humidifiers and air conditioners. While none of these diseases is very common in the general population, their importance stems from their high incidence in particular environments.

Respiratory Failure is a complication of many nonpulmonary diseases. Acute respiratory distress syndromes have been recognized as such only recently. For these two reasons, data on incidence are not available. A conservative estimate is that 150,000 adult cases of acute respiratory distress syndrome occur each year with a mortality rate of 40 percent. These figures do not include failure due to chronic pulmonary disease, (see Emphysema and Chronic Bronchitis), nor do they adequately reflect the true incidence because so many cases are unreported.

BLOOD DISEASES AND BLOOD RESOURCES

Problems of the blood are intimately related to cardiovascular and pulmonary diseases. Blood is a vital part of the circulatory system since it is the vehicle by which oxygen, nutrients, and other body chemicals are carried through the blood vessels to every part of the body, to be exchanged for carbon dioxide, waste products and chemicals which, in turn, need to be transported away from the tissues to other body organs, either for excretion from the body or for use in the life processes.

Three groups of blood problems are defined below: Bleeding and Clotting Disorders, Sickle Cell Disease and Related Disorders of the Red Blood Cell, and Blood Resources.

Bleeding and Clotting Disorders are closely interrelated. Both represent failures in maintaining the blood in an optimal state within the blood vessels. On one hand, failure means bleeding (hemorrhage) into surrounding tissues or outside the body. On the other hand, failure means inappropriate clotting (thrombosis) of the blood within the vessels. Clotting in the arteries deprives a part of the body of its blood supply; clotting in the veins impedes the return of blood to the heart. When excessive clotting affects small blood vessels and capillaries (collectively termed the microcirculation), tissues and cells cannot function well because they are deprived of essential oxygen, energy, regulating hormones and building blocks, and noxious waste products cannot be removed effectively.

The particular portion of the body's defense mechanisms responsible for maintaining the blood in an optimal fluid state is termed the hemostatic system. Excessive bleeding can result from an abnormality or deficiency, acquired or inherited, of any of the elements in the hemostatic system. Bleeding into organs and tissues may impair or destroy their function and uncontrolled, external blood loss may result in death.

The consequences of abnormal clotting depend on the organ or region of the body in which it occurs. In vessels of the heart, brain, lung or other vital organs, the result can be catastrophic; in less vital areas, the effects may be mild and transitory. With time, the clot-dissolving mechanism restores the integrity of the circulation. However, the speed of this process is insufficient in the case of vital organs where even a very brief deprivation of blood supply results in irretrievable loss of function or death of tissue.

The impact of the clotting and bleeding disorders is considerable. Arterial thrombosis causes or complicates a great variety of diseases in all parts of the body; for

example, thrombosis involving the vessels of the kidney contributes to kidney failure, and arterial thrombosis and cerebral hemorrhage play major roles in stroke.

Thrombosis in the veins may produce pulmonary embolism; that is, clot fragments may be carried in the blood from their site of origin to the lungs. About 300,000 persons are hospitalized annually and more than 50,000 die with pulmonary embolism. Clotting in the venous circulation complicates many illnesses and surgical procedures. Autopsy studies show evidence of venous thrombosis in about 50 percent of cases examined, regardless of cause of death.

The microcirculation is a very important component of the circulation system. It conveys to the cells of the body the substances needed for their metabolism and regulation, and carries away their products so that the internal environment is maintained in a manner which allows the cells to survive and perform their interrelated tasks. Bleeding and clotting in the microcirculation are contributory or primary mechanisms in hypertension, stroke, diabetes, infectious and inflammatory disease, autoimmune disease, host-graft rejection, cancer, sickle cell anemia, drug toxicity, mismatched blood transfusion, liver disease, and nephritis. The impact is vast even if it cannot be expressed statistically.

Thrombosis induced by contact of the blood with foreign surfaces remains the major unsolved problem in the development of artificial organs, prosthetic vessels or devices that temporarily assist the circulation.

Excessive blood loss due to inadequate or disturbed function of a component of the hemostatic mechanism is a major cause of death and morbidity in a variety of circumstances such as after severe injury, after surgery, in leukemia, and in cirrhosis of the liver. The threat of hemorrhage limits the aggressive management of some forms of cancer.

The hemophilias are sex-linked, hereditary diseases occurring almost exclusively in males. Although the known hemophilic population of this country is only about 25,000, hemophilia constitutes a major national health problem for two reasons. First, treatment must be continued throughout the lifetime of the patient at enormous cost (the current yearly cost to replace the missing clotting factor alone is estimated to be in excess of $6,000 per patient, or more than $120 million for the 80 percent of hemophiliacs who can benefit from this factor). Second, treatment of the disease presents one of the largest single demands upon the nation's blood resources.

Sickle Cell Disease and Related Disorders of the Red Blood Cell include sickle cell anemia, Cooley's anemia and defects affecting the red blood cell membrane or enzyme systems.

Sickle cell anemia, Cooley's anemia and certain defects affecting the red blood cell membrane or enzyme systems are all genetically determined and are presently incurable, although they may be controlled to varying degrees. These disorders lead to premature destruction of the red cells in the circulation. Anemia results because the bone marrow is unable to produce sufficient numbers of new cells to keep up with the rate of destruction.

Approximately two million individuals, primarily black, carry the sickle cell trait. They are healthy, but if two carriers marry, each of their children has a one in four chance of having sickle cell anemia, a painful and debilitating disorder. About one in 400 black babies in this country is born with sickle cell anemia, and somewhat less than 50,000 individuals suffer the painful episodes known as "crises."

The cost of caring for a patient with sickle cell disease may approach $2,500 to $5,000 a year. The loss of time from school, from jobs and the resultant psychological and educational problems, make this disorder one of high social and economic importance.

Cooley's anemia results from defective production of one of the subunits of the hemoglobin molecule, leading to rapid destruction of the red cells. It occurs in perhaps 5,000 Americans, largely of Mediterranean ancestry. Its victims suffer profound anemia and require repeated blood transfusions for survival. As with the sickle cell trait, carriers do not have symptoms, but offspring may be affected.

Defects in red cell membranes and red cell enzymes also produce anemia. Such defects are relatively rare, although one, called glucose-6-phosphate dehydrogenase deficiency (G6PD), occurs in about 10 percent of black males and less frequently in males of Mediterranean ancestry. Most of these individuals are

healthy, but they are sensitive to a variety of commonly used drugs and may develop anemia if they take them. They also develop anemia with certain illnesses.

Blood Resources for the nation need to be available in an adequate supply. High quality blood and blood products is essential for the effective treatment of many diseases. Whole blood is made up of cellular elements dispersed in a fluid medium called plasma. The cells consist of red cells to deliver oxygen, platelets to stop bleeding, and white cells to fight infection. Plasma contains such useful products as albumin, immunoglobulins, and clotting factors.

To give the patient enough of what he needs and when he needs it requires recruiting the donor, collecting his blood, separating it into its components, detecting and eliminating disease-causing agents, matching the components for compatibility, and administering it to the patient in a fail-safe fashion.

In the United States, an assemblage of organizations (which might be referred to as the blood service complex) acquires, processes, stores, delivers and administers blood and a variety of blood products. This complex has an estimated gross annual income exceeding $500 million. It collects about nine million pints of blood per year for transfusion. About 25 percent of this blood is never transfused and much of this portion is wasted.

Whole blood is mostly collected by the blood-banking sector of the complex. In addition, the pharmaceutical industry, which comprises the other major sector, collects about 1.7 million liters of plasma each year, mainly for the preparation of plasma fractions (about one liter of plasma is present in five units of whole blood).

Transfusion is not without dangers, one of which is the possibility of hepatitis. Approximately 10 to 15 percent of the whole blood collected by the blood-banking sector is obtained from commercial donors. This blood accounts for about a quarter to a half of the incidence of post-transfusion hepatitis. While nationwide reporting of hepatitis of any origin or type is unreliable, it is estimated that each year post-transfusion hepatitis accounts for 850 deaths, 17,000 episodes of illness which are often incapacitating for weeks to months, and another 100,000 infections without symptoms. If we consider only the patients who become ill, their average hospital stay is 28 days. The dollar cost to the nation approximates $86 million per year; costs in terms of human suffering are immeasurable.

Definitions of two additional lung disease problems--Pulmonary Vascular Diseases and Inhalation Diseases--are given below.

Pulmonary Vascular Diseases include cor pulmonale, pulmonary hypertension, and pulmonary edema. Cor pulmonale refers to enlargement of the heart due to an increased workload of the right ventricle resulting from conditions which affect the pulmonary circulation. Pulmonary hypertension is characterized by elevation of pulmonary arterial pressure above normal levels. The condition is considered primary when found in the absence of cardiac or pulmonary diseases and secondary when associated with these diseases. Primary hypertension may be caused by factors such as high altitude and low oxygen, or ingestion of certain drugs and chemicals; secondary hypertension may result from destruction of the pulmonary vascular bed, congenital heart disease, pulmonary vasoconstriction, or congestive heart failure. Pulmonary edema, difficult to detect early, is a pathologic state in which there is abnormal extravascular storage of fluid in the lung. Reliable data on the incidence and prevalence of these diseases are not available. However, it has been estimated that cor pulmonale alone occurs in 40 percent of cases of emphysema and chronic bronchitis, both of which are chronic respiratory diseases of national impact.

Inhalation Diseases are becoming more prevalent in the United States as industrialization and the technological age progress. Of all occupational illnesses, dust inhalation diseases, or pneumoconioses, are the most serious health problem. The dusts inhaled are so fine that they escape the natural cleansing mechanism of the upper respiratory tract and lodge permanently in the lungs. If exposure is sufficiently high and prolonged, the accumulated particles may cause fibrosis or scarring of the lung tissue and in many cases lead to serious disability and even death. One of the most serious problems in our country today comes from the direct handling of asbestos by some 200,000 workers and by another 3 to 5 million persons who are secondarily exposed to the dust. Asbestos is believed to be a leading factor in the deaths of over 2,000 persons each year in the U.S. The breathing of quartz dust, or silica, is another hazard which gradually causes irreversible damage to the lungs. Of the more than 125,000 workers now engaged in coal mining in the United States, an estimated 10 to 20 percent have Coal Worker's Pneumoconiosis, or "black lung." Beryllium, iron, tin, and barium dusts are also hazardous to the lung tissue. Pneumoconioses are also caused by organic dusts from plants such as cotton (byssinosis), sugar cane (bagassosis), and moldy hay (Farmer's lung).

Definitions of Circulatory Assistance, Respiratory Assistance, and Biomaterials, three of the 22 major program elements, are given below.

Circulatory Assistance to the failing heart may be provided by mechanical circulatory devices which aid or replace the pumping action of the heart. There are many types of such devices under development. Some are applied externally to the lower extremities in synchrony with the heart beat.

In others, the pumping action of the heart is enhanced by synchronously expanding and collapsing a "balloon" positioned in the aorta, the artery leading from the heart. On a very limited scale, a few devices have been employed which require substantial surgery and the actual positioning of a pumping device within the chest. While circulatory assist devices are designed to improve the mechanical function of the heart, the apparatus generally involves important electronic, pneumatic, hydraulic, and mechanical systems as well.

Respiratory Assistance can be provided by mechanical devices (ventilators or membrane oxygenators) that support the gas transfer functions of the lung when, as a consequence of disease, the lungs are unable to maintain proper levels of oxygen and carbon dioxide. Ventilators are devices that mechanically inflate the lungs and can deliver increased amounts of oxygen. Membrane oxygenators are externally placed "artificial lungs" which are connected with the patient's circulatory system. Blood from the patient enters the oxygenator, carbon dioxide is removed, the blood is oxygenated and then returned to the patient's circulatory system. At present, oxygenators can only be used safely for several days. Recent experience suggests that this method of respiratory assistance holds promise for treatment of some patients in acute respiratory failure.

Biomaterials are synthetic materials which can be implanted in the body and used in a variety of medical devices. To be "blood compatible," such materials must not cause damage to the various components of blood and must not induce blood to clot. In addition, biomaterials must possess specific properties suited for specialized functions (for example, gas permeability for oxygenation devices) and have minimal risk of causing chemical toxicity, allergic reactions, and neoplasia. Several approaches are being pursued in the development of suitable biomaterials. Properties of the vessel wall have been imitated by "hydrogels," a network structure of long polymer chains and water. Blood compatible surfaces can be grafted or bonded to a variety of materials which have otherwise promising physical properties. Another approach involves the use of human cells which can be grown in culture and attached to certain man-made materials to make them compatible with blood. Materials can be synthesized which contain anticoagulants, clot-dissolving enzymes, and surface-active agents. Composite materials can be produced which are based on a variety of components mentioned above.

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